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MEDICAL DEPARTMENT  
UNITED STATES ARMY  
IN WORLD WAR II





MEDICAL DEPARTMENT, UNITED STATES ARMY

*PREVENTIVE MEDICINE IN WORLD WAR II*

Volume VII

COMMUNICABLE DISEASES

*Arthropodborne Diseases Other Than Malaria*

Prepared and published under the direction of  
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## PREVENTIVE MEDICINE IN WORLD WAR II

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VOLUME VII

Volume VII

# COMMUNICABLE DISEASES

## Arthropodborne Diseases Other Than Malaria





# MEDICAL DEPARTMENT, UNITED STATES ARMY

The volumes comprising the official history of the Medical Department of the United States Army in World War II are prepared by The Historical Unit, United States Army Medical Service, and published under the direction of The Surgeon General, United States Army. These volumes are divided into two series: (1) The administrative or operational series; and (2) the professional, or clinical and technical, series. This is one of the volumes of the latter series.

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## Foreword

The publication of this volume on Arthropodborne Diseases Other Than Malaria completes the preventive medicine discussion on communicable diseases in this historical series of World War II.

In chapter I, Introduction, the late Dr. Henry S. Fuller, Chief of the Department of Rickettsial Diseases at the Walter Reed Army Institute of Research, Washington, D.C., has stated succinctly many of the outstanding matters about which I would comment had not Doctor Fuller already done so in a practical, down-to-earth manner. He has splendidly set the keynote for the succeeding chapters in this book. Throughout the entire volume the reader will likely hold in one hand at all times the potential hazard of infection with arthropodborne disease, while in the other he holds the key to either success or failure—the effectiveness of military preventive medicine.

As is true with all volumes which have been published in the historical series of the Medical Department, U.S. Army in World War II, the knowledge contained in this book is of great importance today not only to the Armed Forces but also to all of our Nation's health resources, as well as to others who are attempting to preserve the peace and to improve the lot of man in far-flung areas of the world.

To all those engaged in the various health fields and particularly to those whose continuous responsibility it is to maintain and improve the health of our military and civilian personnel, at home and abroad, this volume is of inestimable value. For those personnel of our military, of other governmental agencies and of privately supported medical activities who are now or at some future period may be engaged in furthering the general advancement of our people-to-people program in those areas of the world which we think of as underprivileged, and for which great efforts are being made to improve their national health and well-being, this volume should be an essential text. Medical officers and practicing physicians in the fields of preventive medicine and internal medicine will wish to consult and read this text which, although historical, is a gold mine of information of current value.

As I read the book manuscript, I was impressed again and again, as I have been many times during my own long military career—and particularly in my position as The Surgeon General which has required extensive travel to many areas of the earth—with the existing and potential incidence of the arthropodborne diseases amongst the populations of a large part of the world, including the so-called developed nations. We in the Army Medical Service, as well as in our sister services, have given great thought and attention to these health and military problems. These diseases have occupied the time and best efforts of many in our field surveys, research laboratories, hospitals and dispensaries,



classrooms and boards and committees of medical experts. This is equally true of the higher offices of Government and the halls of Congress. To the latter we are deeply grateful for the understanding appropriation of funds for the continuation of many studies and research begun before, or during, World War II, or continued thereafter and directed toward the eradication or control of such devastating diseases as epidemic and murine typhus fevers, scrub typhus, dengue, plague, yellow fever, filariasis, and others.

When confronted with these conditions in World War II, many medical officers had no real previous clinical experience with them. Old knowledge had to be relearned, new knowledge had to be gained, and both had to be applied in the situations at hand. Likewise, it was with commanders of small and large bodies of troops who failed at first to take seriously the actual impact which these diseases could and would have upon the combat effectiveness of their troops. It was imperative that both medical officers and commanders be oriented and indoctrinated accordingly.

The farsightedness which the late Brig. Gen. James Stevens Simmons, wartime Chief of the Army's Preventive Medicine Service and Dr. Francis G. Blake, Dean of the School of Medicine, Yale University, demonstrated in establishing the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army (later called the Army Epidemiological Board) went far in providing the expert assistance in the direction and control of many of these conditions. Various members of this Board and its component commissions conducted invaluable field work in practically all areas of the world where our troops were located, as well as in many university laboratories, making possible the technical knowledge which was then, and is now, utilized by the Medical Department personnel in the recognition, the control, and the treatment of these diseases. Too much cannot be said in recognition of and for the positive contributions made by the Army Epidemiological Board and also the United States of America Typhus Commission, the latter being established by Executive order of President Roosevelt in December 1942. It was most appropriate for Brig. Gen. Stanhope Bayne-Jones, MC, USAR (Ret.), to discuss the activities of this most important body in chapter X of this book. No discussion of typhus fevers in World War II could be complete without an account of the active role undertaken by the Typhus Commission. The uniqueness of its organization, its personnel of highest professional caliber, and the control and operation with full support from highest governmental circles made possible a most effective agency in the control of typhus fever. General Bayne-Jones writes not only from a background complete with knowledge of the typhus fevers, but also as a former member of this Commission of which he was the Director from 1943 to 1946, when it was disbanded.

This volume, written as it has been by 10 established authorities, is one of the most interesting, readable, as well as informative, medicomilitary histories which I have had the opportunity to review and for which I have had the pleasure of preparing a foreword. Although I have devoted most of my pro-



fessional life to the practice of general surgery, I found myself deeply engrossed in the presentations contained in this book—perhaps because in my present role many of the diseases discussed here have far-reaching implications today in our efforts to gain and support the freedom of all peoples throughout the world.

With this volume in print, a commendable contribution to medicomilitary history, and to medical literature in general, has been made. To the authors and editors, to The Historical Unit, U.S. Army Medical Service, and to all others who have made this possible, our grateful appreciation is expressed.

LEONARD D. HEATON,  
*Lieutenant General,*  
*The Surgeon General.*



## Preface

From the beginning of recorded military history, armies at war have been afflicted by diseases borne by insects, mites, ticks, and fleas belonging to the animal phylum Arthropoda. Malaria and other arthropodborne diseases have constituted an enemy on an additional front, one which often wreaked more havoc than the human enemy.

In volume VI of this series, the story of malaria control in World War II has been told. The present volume is concerned with other diseases borne by arthropods and with the measures taken to minimize their impact upon military operations. The general success of the U.S. Army's measures in preventing the arthropodborne diseases, in spite of their frequently high incidence in neighboring civilian populations, speaks eloquently for the value of the control programs. These included the development and use of insecticides, surveys, chemotherapy, and other measures. This general success points up the necessity for continued vigilance and further research.

The authors who have undertaken the task of preparing the chapters in this volume have striven to record accurately the failures as well as the successes in the difficult fight against the arthropodborne diseases during World War II. They have covered their subjects from the standpoint of their own actual experience. Grateful appreciation is expressed to them for their cooperation. Thanks are also extended to all of those who reviewed the chapters and made valuable suggestions to the authors. For this essential help, thanks are expressed to: Dr. Justin M. Andrews, Dr. Stanhope Bayne-Jones, Dr. Lowell T. Coggeshall, Dr. Quentin M. Geiman, Dr. John E. Gordon, Dr. William MacDowell Hammon, Mr. William A. Hardenbergh, Col. Gottlieb L. Orth, MC, USA, Dr. John R. Paul, Dr. Thomas B. Turner, Dr. Thomas G. Ward, and Dr. Andrew J. Warren. The interest and support of the late Dr. Francis G. Blake and the late Dr. Elliott S. A. Robinson are recorded here with gratitude.

This present volume, as well as the others in the Preventive Medicine series, is the outcome of the planning, direction, and detailed concern of members of the Editorial Advisory Board individually and as a body. Dr. Stanhope Bayne-Jones, Chairman of the Board, has brought to bear upon this volume his own significant experiences in the preventive medicine program during World War II. In writing and reviewing and in his detailed scrutiny of the entire volume, Dr. Bayne-Jones has contributed immeasurably to its content. The editors and readers are deeply indebted to him. Dr. Paul F. Russell, member of the Editorial Advisory Board, not only participated as a consultant to volume VI on malaria but has also reviewed in detail each chapter of the present volume. Grateful thanks are extended to him.

The Editorial Office for the preparation of the preventive medicine history is situated at the Medical College of Virginia, in Richmond, and functions under a contract with the Office of The Surgeon General. The editors express their appreciation to the President, the Comptroller, and other officers of the Medical College for their cooperation which has made possible the work of this office. The Editor of the preventive medicine series records his appreciation of the achievements of Col. John Boyd Coates, Jr., MC, USA, Editor-in-Chief and Director of The Historical Unit, U.S. Army Medical Service. In the task of preparing the comprehensive history of the Medical Department, U.S. Army, World War II, of which this series is a part, Colonel Coates is making a valuable contribution to modern medical literature.

The authors and editors have again greatly relied upon the services of the Medical Statistics Division of the Office of The Surgeon General. Mr. E. L. Hamilton, Chief, and Mr. M. C. Rossoff, Assistant Chief, Statistical Analysis Branch, have not only provided essential data but have also checked and reviewed all statistical information in this volume. Their contribution has been a substantial one. The Scientific Illustration Division, Medical Illustration Service, Armed Forces Institute of Pathology, under the direction of Mr. Herman Van Cott, prepared the illustrations for this volume. Maps were prepared by Miss Elizabeth P. Mason, Chief, Cartographic Section, and Miss Jean A. Saffran, Cartographic Draftsman, of the Special Projects Branch, The Historical Unit. Research assistance was rendered by Mrs. Claire M. Sorrell, Historian, of the General Reference and Research Branch, The Historical Unit.

The editors gratefully acknowledge the assistance of Mrs. Marjorie G. Shears, Editor, of the Editorial Branch, The Historical Unit, who performed the publication editing and prepared the index for this volume.

EBBE CURTIS HOFF, Ph. D., M.D.



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## CHAPTER I

# Introduction

*Henry S. Fuller, M.D.*

Humanity has but three great enemies: Fever, famine and war; of these by far the greatest, by far the most terrible, is fever. \* \* \* as far back as history will carry us, in ancient Greece, in ancient Rome, throughout the Middle Ages, down to our own day, the noisome pestilence, in whatsoever form it assumed, has been dreaded justly as the greatest of evils.—Osler, 1896.

The main groups of arthropods of military significance are the same as those which are important as vectors of disease among civilians and lower animals. These insects are certain mosquitoes, sandflies, lice, ticks, and mites. Of these, the mosquitoes, carriers of malaria, yellow fever, dengue, some types of encephalitis, and filariasis, are transmitters of the greatest number and amounts of noisome pestilences in this category. Furthermore, of the diseases in this group, malaria outranks all the rest. Indeed, malaria was so prevalent and so devastating among troops in the Pacific areas, the Far East, and the Mediterranean region during World War II that an entire volume<sup>1</sup> in this series was required for adequate presentation and discussion of its varied, extensive and important problems, and the fight waged against malaria.

The present volume, therefore, deals with the arthropodborne diseases other than malaria, and other than tularemia, which although tickborne in some instances happened to be included among the communicable diseases discussed in another volume<sup>2</sup> at an early time in the planning of this series, because of emphasis of transmission by contact. While malaria is not one of the subjects of this book, brief reference to past experience with it must be made here to establish perspective.

The U.S. Army entered World War II with prior experience in mosquito-borne and louseborne diseases. During the calendar year 1898, which included the Spanish-American War (24 April–10 December 1898), there were recorded<sup>3</sup> the following insect-borne diseases in the Army: Malaria, 90,416 cases; yellow fever, 1,169 cases; and dengue, 249 cases, with fatality rates per 1,000 cases of 4, 123, and 8, respectively. As is well known, yellow fever was the great killer, and this fact has obscured the important role played by malaria.

<sup>1</sup> Medical Department, United States Army. Preventive Medicine in World War II. Volume VI. Communicable Diseases: Malaria. Washington: U.S. Government Printing Office, 1963.

<sup>2</sup> Medical Department, United States Army. Preventive Medicine in World War II. Volume V. Communicable Diseases Transmitted Through Contact or By Unknown Means. Washington: U.S. Government Printing Office, 1960, pp. 131–138.

<sup>3</sup> Report of The Surgeon General, U.S. Army. Washington: Government Printing Office, 1900–1901.

In 1899, the year following that war, malaria continued to produce the highest morbidity rate, while yellow fever produced 262 cases with a fatality rate of 210 per 1,000.

Three insect-borne diseases are recorded <sup>4</sup> for U.S. troops in World War I. Again malaria takes first place with 16,930 recorded cases and with high attack rates for troops stationed in the United States, Panama, and the Philippines. Trench fever made its debut in military medicine in World War I, with 901 cases recorded for the American Expeditionary Forces in Europe. The third insect-borne disease of World War I was classical, louseborne, epidemic typhus, with 47 reported cases. Thus, prior to World War II, malaria, yellow fever, dengue, trench (Volhynia) fever, and epidemic typhus were the arthropodborne diseases with which the Army Medical Corps had had firsthand experience. It follows, therefore, that our Army's practical experience in dealing with vectors was virtually limited to certain of the anopheline vectors of malaria, the culicine vectors of yellow fever and dengue, and the body louse which transmits trench fever and epidemic typhus.

The arena of World War II, comprising all of the major land masses and many islands from the smallest to the largest in size, saw our troops exposed for the first time, in unfamiliar surroundings, to a wide variety of infectious diseases. The hazard of infection was often unknown to the troops, their medical officers seldom had had previous clinical experience with such problems, and most of the military entomologists were meeting vectors new to them. The results of mass exposure of the Army to infected vectors are indicated approximately in table 1.

In introducing this history, it is useful to consider military problems in arthropodborne disease from the distinctly different standpoints of the line officer, the medical officer, and the entomologist.

The field commander encountered our present group of diseases in several types of setting. During training and staging operations, for example, filariasis was important in troops being readied in American Samoa for the assault on enemy-held islands in the Pacific. The fear of contracting this infection, in particular the horror of elephantiasis as a possible consequence, severely affected the morale of men who were shocked by the sight of natives whose scrotums were enormous. The fear of sterility was enhanced by the knowledge that there was no effective drug for treatment of filariasis. It seems probable to this author that the fear motivation—fundamentally undesirable though it be—prompted men to cooperate in measures designed to control mosquitoes, to prevent mosquito bites, and to avoid contact with indigenes, although soldiers are not usually afraid of contact with local inhabitants as indicated by the large number of cases of venereal disease in all theaters.<sup>5</sup>

<sup>4</sup>(1) The Medical Department of the United States Army in the World War. Washington: U.S. Government Printing Office, 1928, vol. IX, pp. 483, 485, and 513. (2) The Medical Department of the United States Army in the World War. Washington: Government Printing Office, 1925, vol. XV, pt. 2, pp. 580-669.

<sup>5</sup>Medical Department, United States Army. Preventive Medicine in World War II. Volume V. Communicable Diseases Transmitted Through Contact or By Unknown Means. Washington: U.S. Government Printing Office, 1960, pp. 139-341.

TABLE 1.—*Estimated incidence and deaths, and case fatality rate, due to arthropodborne diseases in the U.S. Army, 1942-45*

[Preliminary data based on tabulations of individual medical records]

Disease	Incidence (number)	Deaths (number)	Fatality rate per 1,000 cases
Malaria.....	378, 000	302	0. 8
Dengue.....	91, 000	4	0. 0
Sandfly fever.....	19, 000	0	0
Scrub typhus.....	5, 400	283	52. 4
Filariasis.....	<sup>1</sup> 2, 500	1	. 4
Murine typhus.....	800	15	18. 8
Leishmaniasis.....	500	0	0
Encephalitis.....	<sup>1</sup> 400	21	52. 5
Tularemia.....	200	4	20. 0
Relapsing fever.....	170	0	0
Rocky Mountain spotted fever.....	130	12	92. 3
Epidemic typhus.....	100	0	0

<sup>1</sup> Admissions only, data on secondary diagnosis cases are not available for 1942 and 1943.

Source: Tables of incidence and deaths from "Infectious and Parasitic Diseases in the United States Army During World War II. Each Theater by Specific Disease and Year." Department of the Army, Office of The Surgeon General, Medical Statistics Division, 26 July 1954. (Revised to include changes made up to 5 October 1960.) The following notes are quoted from the above-cited volume of statistical tables:

The data are to be considered preliminary pending publication of final tabulations of the individual medical records (p.i).

Caution should be exercised in evaluating the data for low incidence diseases which were based on small (that is, 20 percent) samples (p. ii).

For purposes of this volume, the Mediterranean theater includes North Africa and the North American theater includes Alaska and Iceland (p. iii).

Although the mortality data were based on complete files of individual medical records, they too are to be considered provisional pending publication of final tabulations (p. iii).

The author has used approximate rounded figures extracted from a number of tables in this mimeographed statistical volume.

During and immediately after an invasion, dengue, sandfly fever, and scrub typhus—each in its own locality—caused attack rates which will never be forgotten by the commanders whose troops encountered them. Dengue and sandfly fever struck down many men of invading forces, rendering them noneffective against the usually immune enemy force, who were immune because they had suffered their attacks several months or years previously. Thus, the invading force was severely handicapped by disease during the critical period of landing, and establishing a beachhead, even before it had an opportunity to proceed with the business of securing the hinterland. Dengue and sandfly fever struck like lightning, inflicting serious inroads during the first week of exposure. Scrub typhus, with its longer average incubation period and more insidious onset, began to make known its presence during the second, third, and subsequent weeks of a campaign. For its military significance, every line officer should be familiar with the outbreak at Sansapor, New Guinea (ch. XI), in which scrub typhus rendered a regiment ineffective more quickly and thoroughly than would have been expected as a result of severe enemy action.



The aforementioned examples can be multiplied manyfold. The lessons learned should be pondered by every line officer and carried out accordingly.

The medical officer, knowing full well that the statistics in table 1 are subject to numerous fallacies, realizes that the numbers, in themselves, are no indication of the severity of a particular disease problem at a given time and place. Malaria, of all the arthropodborne diseases affecting the Army in World War II, was of paramount importance for approximately one-fourth of the earth's human population lives in malarial zones, and our troops were present in most of the places where malaria flourishes.

In terms of locality, the Southwest Pacific theater recorded the greatest numbers of admissions for arthropodborne disease, ranking number one in this respect, with the rank of the other theaters as follows: Second, Central and South Pacific; third, China-Burma-India; fourth, Mediterranean; fifth, continental United States; sixth, Europe; seventh, Latin America; eighth, Middle East; and ninth, North America. The same order of rank of theater was observed for malaria admissions with the exception that continental United States ranked fourth and China-Burma-India ranked fifth. For dengue, the rank of theater by admissions was as follows: First, Southwest Pacific; second, Central and South Pacific; third, Mediterranean; and fourth, China-Burma-India. For sandfly fever, the rank of theater by admissions was as follows: First, Mediterranean; second, Middle East; third, China-Burma-India; and fourth, Europe.

Scrub typhus produced the following rank of theaters by admissions: First, Southwest Pacific; second, China-Burma-India; and third, Central and South Pacific. Filariasis produced the following rank of theaters by admissions: First, Central and South Pacific; second, continental United States (not autochthonous, but diagnosed by blood smear of troops evacuated from overseas); and third, Southwest Pacific. Murine typhus occurred as follows: First, continental United States; and second, Central and South Pacific. Leishmaniasis, almost solely cutaneous, was a problem of the Middle East. Encephalitis, which is a heterogeneous assemblage including entities not transmitted by arthropods, was reported mainly from the continental United States. Rocky Mountain spotted fever was reported solely from the continental United States. The remainder of the diseases in table 1—tularemia,<sup>6</sup> relapsing fever (ch. VIII), and epidemic typhus (ch. X)—occurred in small numbers of cases.

The values given for incidence rates for arthropodborne diseases in the U.S. Army (table 2) are at once illuminating to those who saw active service in one or more of these theaters, and shocking to those who did not. These rates reflect the interplay between at least two factors, each operating to an extent which is difficult to evaluate for any given theater. One factor is the amount of potential hazard of infection with arthropodborne disease, while the other is the effectiveness of military preventive medicine. Although the degree of hazard can be stated in rough, comparative terms, it is virtually im-

<sup>6</sup> See footnote 2, p. 1.



possible to “measure” by reason of the multiplicity of factors involved. It requires little erudition to state that the hazard of arthropodborne disease was, generally speaking, less in Alaska than it was in the China-Burma-India theater; it is undoubtedly relevant to note that a Theater Preventive Medicine Section was formed in China-Burma-India, for the first time, in late 1944. Within that theater, the risk of infection, for example, with scrub typhus was nil for personnel who were not exposed to the vector species of chiggers. For those engaged in actual combat in Burma, the hazard was extremely high, as evidenced by excessive attack rates in Merrill’s Marauders and the Mars Task Force during 1944 and 1945, respectively. Similar examples can be cited for this and other arthropodborne diseases in various theaters. That the rates were no higher than they were can be ascribed, in part, to the application of appropriate preventive measures. However, all the advice and recommendations will be ineffectual if the individual combatant does not comprehend in some degree the reasons for their application, and so assist in their being carried out. Although these troops were provided with repellent, which kills the chigger vectors when used properly, they discarded this material as well as other equipment which they did not consider essential to their survival in combat.

TABLE 2.—Incidence rates for arthropodborne diseases in the U.S. Army, by theater or area of admission, 1942-45

[Preliminary data based on tabulations of individual medical records]  
[Rate expressed as number of cases per annum per 1,000 average strength]

Rank	Theater or area	Rate
1-----	China-Burma-India-----	114. 69
2-----	Middle East-----	97. 85
3-----	Southwest Pacific-----	87. 59
4-----	Central and South Pacific-----	86. 83
5-----	Mediterranean-----	50. 58
6-----	Latin America-----	42. 76
7-----	Europe-----	4. 99
8-----	Continental United States-----	3. 12
9-----	North America-----	. 39
	Total Army-----	19. 56

Source: Medical Department, United States Army. Preventive Medicine in World War II. Volume IV. Communicable Diseases Transmitted Chiefly Through Respiratory and Alimentary Tracts. Washington: U.S. Government Printing Office, 1958, p. 45.

With respect to mortality, it is clear that the greatest numbers of deaths from arthropodborne disease were caused by malaria and scrub typhus. In view of the availability of effective, specific antimalarial drugs, it seems fair to conclude that the deaths attributed to malaria—if correctly so—were preventable. Such was not the case with scrub typhus. As pointed out by Gor-

don,<sup>7</sup> the annual death rate of 14.6 per 100,000 for scrub typhus in the China-Burma-India theater topped that of any other communicable disease in any theater of World War II. Fortunately, in view of postwar developments in broad spectrum antibiotic chemotherapy, deaths from scrub typhus are now in the preventable category, as are deaths from murine typhus (ch. X) and other rickettsial diseases.

Epidemic typhus, plague, and yellow fever have been among the major pestilences of previous wars. It is noteworthy, therefore, that the U.S. Army in World War II experienced only slightly more than 100 cases of louseborne typhus, while there were no recorded cases of plague or yellow fever. A critical review of the facts presented in this volume leads to the conclusion that this experience in World War II is truly a triumph of military preventive medicine.

When confronted by actual situations involving arthropodborne diseases, the medical officer is often understandably confused, for his prior training, experience, and viewpoint have rarely equipped him to deal with such situations with equanimity. In approaching the subject, therefore, it is helpful for him to bear in mind the following points:

Three general principles govern the efficiency of arthropods as vectors of human disease and of other animal species as reservoirs of infectious agents. They are the character of the existing host-parasite relation between species and infectious agent concerned, the population numbers of vector or animal reservoir, and the relationship to man of the species acting as reservoir or vector. The first is inherently a biologic matter; the other two bring into play the whole ecologic complex. Populations of arthropod vectors and animal reservoirs are intimately related to the physical environment for as the physical environment acts on man as a host, so likewise it affects these other hosts.<sup>8</sup>

One who reflects upon these ecological considerations will realize the complexity of the problem and the consequent requirement for complete cooperation between physician and entomologist.

The entomologist has a primary, indispensable role in the prevention and control of arthropodborne infection. Of the six human diseases subject to international convention, four are arthropodborne: epidemic typhus and relapsing fever, transmitted by human body lice; plague, by certain rodent-fleas; and yellow fever, by certain culicine mosquitoes. This fact alone serves to place these dread diseases in perspective for the medical entomologist.

Of the diseases considered in this volume, effective vaccines for general use are available only for yellow fever, epidemic typhus, murine typhus, and Rocky Mountain spotted fever, while the effectiveness of various plague vaccines continues to be a subject of investigation (ch. VII). For prevention and control of these diseases, however, these vaccines supplement, and do not supplant, vector control, which remains the core of arthropodborne disease control.

<sup>7</sup> Gordon, John E.: General Considerations of Modes of Transmission. *In* Medical Department, United States Army. Preventive Medicine in World War II. Volume IV. Communicable Diseases Transmitted Chiefly Through Respiratory and Alimentary Tracts. Washington: U.S. Government Printing Office, 1958, p. 40.

<sup>8</sup> Gordon, John E.: Ecological Investigation of Disease. *In* Research in Public Health. [Papers presented at the 1951 Annual Conference of the Milbank Memorial Fund.] Milbank Memorial Fund, New York, 1952, pp. 49-65, esp. p. 53.

This fact is emphasized (1) in order to place vector control in perspective in its relation to disease control, and (2) because the folly of neglecting or omitting vector control has been so convincingly demonstrated on so many occasions that the experiment need not be repeated. He who doubts the truth of these statements will do well to ponder the lessons contained in the ensuing pages of this volume.





## CHAPTER II

# Encephalitis

*Albert B. Sabin, M.D.*

### SIGNIFICANCE OF THE TERM "ENCEPHALITIS"

The clinical diagnosis of encephalitis covers a multitude of clinical, pathologic, etiologic, and epidemiologic entities. Clinical records from civilian as well as military medical practice reveal that the diagnosis is commonly made whenever clinical manifestations suggestive of cerebral disturbance (ranging from mild lethargy to coma, from slight delirium to complete disorientation, from restlessness to convulsions) are associated with an otherwise undiagnosable febrile illness. The diagnosis is also not infrequently made when the aseptic meningitis syndrome is associated with what may be interpreted as lethargy or unusual restlessness. It is made not only when cerebral disturbance is associated with pleocytosis, but also in its absence. The clinical diagnosis of encephalitis is not infrequently made when toxic encephalopathy is associated with certain bacterial infections.

The unqualified diagnosis of encephalitis has no significance for either civilian or military epidemiology because it deals with totally unrelated diseases. Unfortunately, neither civilian nor military reporting of encephalitis has as yet required the qualifications which would lend the data any significance. Military preventive medicine and epidemiology are obviously especially interested in the encephalitides which may occur in epidemics. During World War I and in the decade which followed, encephalitis lethargica (von Economo's disease) appeared as an epidemic disease. Between 1930 and 1940, however, this disease became extremely rare, and a new group of epidemic summer encephalitides of diverse virus etiology was recognized as a source of potential danger. The epidemics of St. Louis encephalitis in the St. Louis area in 1933 and 1937; the outbreak of eastern equine encephalitis in human beings in Massachusetts in 1938; the demonstration in 1934 that the oft-recurring epidemics of summer encephalitis in Japan were due to a virus which was related to, though antigenically different from, that responsible for St. Louis encephalitis; the discovery in 1937 of the spring-summer type of encephalitis in the forested far-eastern regions of the U.S.S.R. and the demonstration that it was caused by a new virus which was tickborne—all brought to light new epidemic diseases which were of special concern to the military epidemiologist.

## ENCEPHALITIS DURING WORLD WAR I

There were 80 admissions for encephalitis in the Army between 1 April 1917 and 31 December 1919. Little or nothing is known of the clinical varieties included in this number, but it is noteworthy that 27 deaths occurred, yielding a case fatality rate of 33.8 percent.<sup>1</sup> It is probable that some of these cases were the then newly recognized von Economo's disease.

## ENCEPHALITIS BETWEEN 1920 AND 1940

The Army was apparently little concerned with encephalitis during the 1920-40 period. Although a number of new encephalitic viruses were discovered between 1930 and 1940, the natural history of the infections, particularly as it related to human disease, was still in the earliest stages of investigation and very poorly understood.

It may be recalled that the epidemiologic studies on the 1933 epidemic of encephalitis in St. Louis ended with the conclusion that it was essentially an infection of human beings transmitted by secretions of the upper respiratory tract. Early observations on the western equine encephalitis suggested that the infection may occasionally affect human beings, but no significant epidemics proved to be due to this virus had occurred by the end of the 1930 decade. Experimental work with the viruses of western and eastern equine encephalitis indicated that various species of *Aedes* mosquitoes were capable of transmitting these viruses, but no direct evidence was available that these viruses were arthropodborne. In 1938, however, the occurrence of a small outbreak of encephalitis in human beings in Massachusetts, caused by the virus of eastern equine encephalitis, indicated for the first time that a virus that was hitherto known to be responsible only for encephalitis in horses could also under unpredictable circumstances give rise to an epidemic. The work of Japanese and Russian investigators brought forth suggestive evidence that the virus responsible for Japanese B encephalitis may, under natural conditions, be transmitted by mosquitoes. The discovery of the Russian spring-summer encephalitis and the extra-human reservoir of the virus in ticks, and involvement of various lower animals as part of its natural history, directed new attention to the possible importance of arthropodborne encephalitis viruses for human beings.

## ENCEPHALITIS DURING WORLD WAR II

### Potential Problems and Proposed Research

The work begun in 1941 by Dr. W. McD. Hammon and his associates on the occurrence of the viruses of St. Louis and western equine encephalitis in

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<sup>1</sup> The Medical Department of the United States Army in the World War. Washington: Government Printing Office, 1925, vol. XV, pt. 2, p. 577.

mosquitoes under natural conditions further emphasized the potential significance of arthropodborne viruses as a possible cause of epidemics of encephalitis. During World War II, the Army was particularly concerned with the potential threat of the viruses of equine and St. Louis encephalitis in the United States and of Japanese B encephalitis in the Far East. The Commission on Neurotropic Virus Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army (later Army Epidemiological Board), was charged with the responsibility of furthering research on these viruses. The objectives of this research were as follows: (1) To increase our knowledge of the natural history of these infections with special reference to the role of arthropods; (2) to develop vaccines suitable for human use against the viruses of western equine, St. Louis, and Japanese B encephalitis; and (3) to develop improved and standardized methods of specific serologic diagnosis. The occurrence of the first large epidemic of western equine encephalitis, affecting more than 3,000 human beings (predominantly adults) in Northwestern United States and adjacent Canada during the summer of 1941, was responsible for imparting an urgency to the proposed task.

### Actual Experience During the War

**Incidence and official statistics.**—No epidemics of encephalitis occurred among the Armed Forces in the United States between 1942 and 1945. During July and August 1941, however, 12 mild cases of encephalitis of unestablished etiology developed in a force of unknown size within 10 to 14 days after entry into a maneuver area near Sabinal, Uvalde County, Tex.<sup>2</sup> One small outbreak, identified as Japanese B encephalitis, occurred among American forces in Okinawa in 1945. Small outbreaks of encephalitis of undetermined etiology occurred also in China and the Philippines during the summer of 1945. Hundreds of cases of encephalitis appeared in the periodic summary reports, particularly during 1942–43 in the United States, but in view of the manner in which the diagnoses were made, the significance of the statistics is doubtful. The official statistics for various forms of encephalitis are given in tables 3, 4, and 5. Col. John E. Gordon, MC,<sup>3</sup> however, states that “encephalitis in the European Theater was a rarely recognized condition” and lists only three cases for the entire period of 1942 through 1945.

It is important to note that practically all reports of encephalitis were followed up by requests that specimens of cerebrospinal fluid and blood be sent to the Army Medical School, Washington, D.C., for viral studies. Many of the clinical records of cases diagnosed as encephalitis presented nothing more than the syndrome of aseptic meningitis. The Army's experience with this syndrome (frequently also reported as lymphocytic meningitis or lymphocytic

<sup>2</sup> Woodland, J. C., and Smith, E. M.: Acute Encephalitis: Mild Epidemic Observed at Station Hospital, Fort Sam Houston, Tex. *J.A.M.A.* 120: 358–361, 3 Oct. 1942.

<sup>3</sup> Gordon, John E.: A History of Preventive Medicine in the European Theater of Operations, 1941–45, vol. II, pt. III, p. 50. [Official record.]



TABLE 3.—*Admissions for acute infectious encephalitis (including infectious encephalomyelitis)<sup>1</sup> in the U.S. Army, by theater or area and year, 1942-45*

[Preliminary data based on sample tabulations of individual medical records]  
 [Rate expressed as number per annum per 1,000 average strength]

Theater or area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States.....	187	0.01	44	0.02	65	0.01	43	0.01	35	0.01
Overseas:										
North America <sup>2</sup> .....	0		0		0		0		0	
Latin America.....	3	.01	2	.02	1	.01	0		0	
Europe.....	72	.02	1	.01	6	.02	20	.01	45	.02
Mediterranean <sup>3</sup> .....	39	.03	0		2	0.00	27	.04	10	.03
Middle East.....	1	.01	0		0		1	.02	0	
China-Burma-India.....	25	.06	0		0		5	.03	20	.09
Pacific Ocean Area.....	37	.03	1	.01	4	.01	12	.03	20	.05
Southwest Pacific.....	70	.04	0		1	.01	29	.05	40	.04
Total overseas.....	247	0.02	4	0.01	14	0.01	94	0.02	135	0.03
Total Army.....	434	0.02	48	0.01	79	0.01	137	0.02	170	0.02

<sup>1</sup> Includes admissions for Japanese B type encephalitis. Excludes postvaccinal encephalitis and postvaccinal encephalomyelitis.

<sup>2</sup> Includes Alaska and Iceland.

<sup>3</sup> Includes North Africa.

NOTE.—The strengths on which the rates were based are mean strengths and will vary therefore from the official strength reports of The Adjutant General. Absolute zero is indicated by zero in the units column; 0.0 indicates a rate of more than zero but less than 0.05 and 0.00 a rate of more than zero but less than 0.005.

choriomeningitis) is described by Rasmussen and Smadel.<sup>4</sup> In many other instances, the diagnosis of encephalitis was made in patients with moderate to severe cerebral manifestations during the course of streptococcal or other bacterial infections. Thus, 10 cases of virus encephalitis reported from Truax Army Air Field, Madison, Wis., between 31 January and 20 April 1943, were investigated by Maj. I. Pilot, MC, of the Sixth Service Command Laboratory, who found that they “were largely toxic manifestations of upper respiratory infection or specific exanthemata.”<sup>5</sup> The cerebrospinal fluid of none of these patients exhibited pleocytosis, although in most instances there was an elevation of protein, which in some cases was as high as 143 mg. percent. A study of the clinical records revealed, also, instances of primary nonbacterial encephalitis of undetermined etiology. It is also of particular interest that the virus of herpes simplex was demonstrated to be the etiologic agent in three fatal cases of encephalitis, two originating in the United States and one in

<sup>4</sup> Rasmussen, A. F., Jr., and Smadel, J. E.: Lymphocytic Choriomeningitis. In Medical Department, United States Army. Preventive Medicine in World War II. Volume V. Communicable Diseases Transmitted Through Contact or By Unknown Means. Washington: U.S. Government Printing Office, 1960, pp. 363-366.

<sup>5</sup> Report, Maj. I. Pilot, MC, to Chief, Medical Branch, Sixth Service Command, 24 Apr. 1943, subject: Encephalitis and Respiratory Infections, Truax Field, Madison, Wis.



TABLE 4.—Admissions for encephalitis, other and undetermined,<sup>1</sup> in the U.S. Army, by theater or area and year, 1942-45

[Preliminary data based on sample tabulations of individual medical records]  
[Rate expressed as number per annum per 1,000 average strength]

Theater or area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States.....	831	0.06	255	0.10	300	0.06	181	0.05	95	0.03
Overseas: <sup>2</sup>										
North America <sup>3</sup> .....	12	0.02	3	0.03	8	0.04	1	0.01	0	0
Latin America.....	3	.01	0		3	.02	0		0	0
Europe.....	59	.01	7	.08	7	.03	15	.01	30	.01
Mediterranean <sup>4</sup> .....	85	.06	4	.17	50	.11	21	.03	10	.03
Middle East.....	4	.03	0		4	.08	0		0	0
China-Burma-India.....	22	.05	2	.23	0		15	.09	5	.02
Pacific Ocean Area.....	37	.03	4	.03	14	.05	9	.02	10	.03
Southwest Pacific.....	69	.04	3	.04	1	.01	5	.01	60	.06
Total overseas.....	296	0.03	23	0.04	87	0.05	66	0.02	120	0.03
Total Army.....	1,127	0.04	278	0.09	387	0.06	247	0.03	215	0.03

<sup>1</sup> Excludes: Postvaccinal encephalitis and postvaccinal encephalomyelitis; acute infectious encephalitis; and encephalomyelitis, other and undetermined.  
<sup>2</sup> Includes admission on transports for 1945.  
<sup>3</sup> Includes Alaska and Iceland.  
<sup>4</sup> Includes North Africa.

NOTE.—The strengths on which the rates were based are mean strengths and will vary therefore from the official strength reports of The Adjutant General.

Absolute zero is indicated by zero in the units column; 0.0 indicates a rate of more than zero but less than 0.05 and 0.00 a rate of more than zero but less than 0.005.

Brisbane, Australia.<sup>6</sup> A fatal case of encephalitis in a U.S. Navy seaman in Trinidad in 1943 was proved to be due to the virus of Venezuelan equine encephalitis.<sup>7</sup>

**Japanese B encephalitis on Okinawa in 1945.**—The first experience of American Armed Forces with Japanese B encephalitis was described in detail in a publication by this author.<sup>8</sup> Here, only the facts of special interest to military preventive medicine will be recorded. An epidemic of the disease, affecting the native population, began early in July and ended early in September 1945. The etiology of the “summer encephalitis” occurring on Okinawa was definitely established for the first time as being due to the virus of Japanese B encephalitis by both serologic methods and recovery of the virus from a fatal case. Almost the entire native population (several hundred thousand)

<sup>6</sup>(1) Zarafonets, C. J. D., Smadel, J. E., Adams, J. W., and Haymaker, W.: Fatal Herpes Simplex Encephalitis in Man. *Am. J. Path.* 20: 429-445, May 1944. (2) Whitman, L., Wall, M. J., and Warren, J.: Herpes Simplex Encephalitis: A Report of Two Fatal Cases. *J.A.M.A.* 131: 1408-1411, 24 Aug. 1946.  
<sup>7</sup> Randall, R., and Mills, J. W.: Fatal Encephalitis in Man Due to the Venezuelan Virus of Equine Encephalomyelitis in Trinidad. *Science* 99: 225-226, March 1944.  
<sup>8</sup> Sabin, A. B.: Epidemic Encephalitis in Military Personnel; Isolation of Japanese B Virus on Okinawa in 1945, Serologic Diagnosis, Clinical Manifestations, Epidemiologic Aspects and Use of Mouse Brain Vaccine. *J.A.M.A.* 133: 281-293, February 1947.

TABLE 5.—*Admissions for encephalomyelitis, other and undetermined,<sup>1</sup> in the U.S. Army, by theater or area and year, 1942-45*

[Preliminary data based on sample tabulations of individual medical records]  
 [Rate expressed as number per annum per 1,000 average strength]

Theater or area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States.....	122	0.01	17	0.01	55	0.01	30	0.01	20	0.01
Overseas: <sup>2</sup>										
North America <sup>3</sup> .....	2	0.00	0		1	0.01	1	0.01		0
Latin America.....	1	0.00	0		1	.01	0			0
Europe.....	30	.01	2	.02	3	.01	5	0.00	20	.01
Mediterranean <sup>4</sup> .....	23	.02	1	.04	7	.02	15	.02		0
Middle East.....	0		0		0		0			0
China-Burma-India.....	5	.01	0		0		5	.03		0
Pacific Ocean Area.....	0		0		0		0			0
Southwest Pacific.....	32	.02	0		2	.01	5	.01	25	.02
Total overseas.....	98	0.01	3	0.01	14	0.01	31	0.01	50	0.01
Total Army.....	220	0.01	20	0.01	69	0.01	61	0.01	70	0.01

<sup>1</sup> Excludes postvaccinal encephalomyelitis and infectious encephalomyelitis.

<sup>2</sup> Includes admissions on transports for 1945.

<sup>3</sup> Includes Alaska and Iceland.

<sup>4</sup> Includes North Africa.

NOTE.—The strengths on which the rates were based are mean strengths and will vary therefore from the official strength reports of The Adjutant General.

Absolute zero is indicated by zero in the units column; 0.0 indicates a rate of more than zero but less than 0.05 and 0.00 a rate of more than zero but less than 0.005.

and their domestic animals had been moved to the northern portion of the island and crammed, under primitive conditions, into an area previously inhabited by possibly from 20,000 to 40,000 persons. A military force of approximately 250,000 was in readiness for the forthcoming invasion of Japan. No one could predict the incidence of this disease in this previously unexposed, presumably fully susceptible, military population. Although antimosquito measures were immediately intensified, it was also clear that this was a situation which called for the utilization of the Japanese B encephalitis vaccine, which had been developed and prepared in large amounts for just such an emergency. However, the events which followed illustrated the practical difficulties that are encountered in the administration of a large-scale vaccination program in the face of a developing epidemic.

On 12 July 1945, within 2 days after the outbreak was recognized, the preventive medicine officers on the island appealed by radio for enough vaccine to inoculate the entire force. In view of the possible need of the vaccine for combat troops scheduled for the imminent assault against the main islands of Japan, this request was not quickly granted. By the end of July, when only about 800 to 1,000 (predominantly military government officials in intimate association with the native population) had been inoculated, the local command was requested to use the vaccine only for combat troops under combat condi-

tions. In the meantime, almost all febrile central nervous system illnesses of undetermined etiology were regarded as instances of Japanese B encephalitis, and a number of such cases began to occur among military personnel. Accordingly, at a meeting of Army and Navy medical authorities of the Island Command, the decision was reached to resume vaccination, inoculating troops radially from known foci of infection. Since all cases of the disease among the native and military populations occurred in the northern part of the island, at least two-thirds of the total military force remained unvaccinated. Vaccination proceeded irregularly, and it was not until 21 August that all units north of Ishikawa were ordered to be inoculated. Enough vaccine was ultimately distributed for inoculation of about 77,000 men.

Between early July and mid-September, 38 military patients, exhibiting a variety of clinical manifestations, were investigated by serologic methods for evidence of infection with the virus of Japanese B encephalitis. Of these, only 11 yielded unequivocal evidence of the specific infection; all of these were unvaccinated and presented moderate to severe clinical signs of cerebral involvement. Two of the eleven died, and autopsy revealed diffuse cerebral lesions compatible with a diagnosis of viral encephalitis. Of this group of 11 patients, 8 had onset of disease between 18 July and 11 August, 1 on 15 August, and 2 on 21 August. Among the remaining 27 patients, there were only 2 who exhibited complement-fixing antibodies for the Japanese B virus. Like others in this group, without any serologic evidence of infection with the Japanese B virus, these two patients presented only a mild, aseptic meningitis syndrome, and since both had received vaccine shortly before they became ill, it is possible that the antibody response was caused by the vaccine rather than by infection. Tests carried out the following year on 24 American soldiers inoculated with the same type of vaccine showed that 2 developed complement-fixing antibodies of the same order of magnitude found in these 2 patients.<sup>9</sup>

Thus, it can be said that only 11 military personnel were unequivocally affected by the virus during the entire Okinawa epidemic, and one naturally wonders to what extent the antimosquito measures and the vaccination might have been responsible for this low incidence. Since not a single case of the disease developed among the more than two-thirds of the total force of approximately 250,000 men which occupied the southern portion of the island and remained unvaccinated, it would appear that a susceptible military force sufficiently removed from the native population and its domestic animals is not endangered by this infection.

The serologically proved military cases acquired their infection in the extreme northern portions of the island, where mosquito control was rendered difficult by the mountainous terrain. It is significant that in these same areas an outbreak of malaria due to *Plasmodium vivax* affected from 6,000 to 8,000 natives, as well as several hundred troops, during the same period as the en-

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<sup>9</sup> Ginder, D. R., Matumoto, M., Schlesinger, R. W., and Sabin, A. B.: Neutralizing and Complement-Fixing Antibodies for Japanese B Encephalitis Virus in Vaccinated U.S. Personnel in Japan. Proc. Soc. Exper. Biol. & Med. 65: 130-140, May 1947.



cephalitis was in progress.<sup>10</sup> It is also of interest that while most of the military government people were vaccinated early, that is, before the end of July, the only case of encephalitis among them was in one person who had escaped vaccination. Since the last civilian cases had their onset very early in September (and infection probably at the end of August), it appeared that more than one-half of the inoculated Americans probably received their vaccine after the danger of infection had already passed. The risk of a completely susceptible group, although variable and unpredictable, was apparently not so great as had been feared. An outbreak of Japanese B encephalitis which occurred in Korea in 1946 among 1,500 unvaccinated Americans showed that under certain conditions the incidence may be as high as 1 in 500.<sup>11</sup> If one assumes that the military population risk on the northern portion of Okinawa in 1945 was about 77,000 (the number for which vaccine was issued), the 11 proved cases of the disease yield an attack rate of only 1 in 7,000. Unfortunately, the experience on Okinawa provided no basis for estimating the extent to which vaccination might have been responsible for this low incidence.

**Summer encephalitis among Americans in China in 1945.**—A small outbreak of encephalitis in Americans stationed in the region of Chih-chiang and Chensi, China, occurred in July 1945.<sup>12</sup> Eight patients with severe clinical manifestations of encephalitis were admitted between 13 and 22 July. Two of the eight patients died. In the same general locality and at about the same time, an epizootic of encephalitis affected about 100 horses belonging to the Chinese, with a case fatality rate of about 15 percent. The clinical manifestations in the human cases were identical with those in the serologically unequivocal cases of Japanese B encephalitis which occurred on Okinawa at about the same time. Although no serologic studies are on record for the cases in China, it is highly probable that they might have been caused by the virus of Japanese B encephalitis. Serologic studies carried out in China in 1946 indicated that inapparent forms of infection with the virus of Japanese B encephalitis are very common in the native population.<sup>13</sup>

**Sporadic cases of encephalitis, possibly due to the Japanese B virus in the Philippine Islands.**—During a visit to the Philippines in September 1945, Col. Dwight M. Kuhns, MC, Commanding Officer, 19th Medical General Laboratory, called the author's attention to the fact that cases of encephalitis had been occurring in U.S. Army personnel in various parts of Luzon. In going over the clinical abstracts submitted to the laboratory by several general hospitals, there was no difficulty in selecting at least 25 typical case histories which clinically were identical with those just studied on Okinawa. There

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<sup>10</sup> Medical Bulletin No. 21, Office of the Surgeon, Headquarters, Army Service Command I, 8 Oct. 1945.

<sup>11</sup> Sabin, A. B., Schlesinger, R. W., Ginder, D. R., and Matumoto, M.: Japanese B Encephalitis in American Soldiers in Korea. *Am. J. Hyg.* 46: 356-375, November 1947.

<sup>12</sup> Essential Technical Medical Data, Headquarters, U.S. Army Forces, China Theater, for July 1945, dated 4 Sept. 1945.

<sup>13</sup> Sabin, A. B., Schlesinger, R. W., and Ginder, D. R.: Clinically Apparent and Inapparent Infection With Japanese B Encephalitis Virus in Shanghai and Tientsin. *Proc. Soc. Exper. Biol. & Med.* 65: 183-187, June 1947.



were either no fatalities among them or the fatal cases were reported as polio-encephalitis. The cases had occurred in July and August 1945, and single serum specimens were available on seven patients. However, positive tests for complement-fixing or neutralizing antibodies, or both types, were obtained on all seven sera. Simultaneous tests on five other sera obtained from American patients with other clinical conditions in the same hospitals in the Philippines yielded negative results. Since no Japanese B encephalitis vaccine was used in the Philippines, these results suggested the possibility that the virus of Japanese B encephalitis was also present in the Philippine Islands. Since only a single specimen of serum was available on each patient, a conclusive diagnosis could not be made.<sup>14</sup> Subsequent serologic studies in the Philippines on normal Filipinos and patients with encephalitis, as well as on horses, cattle, and goats, yielded further evidence indicative of the presence of the Japanese B encephalitis virus in the Philippine Islands.<sup>15</sup>

**Postvaccinal encephalitis.**—It is estimated that at least 10 million individuals were vaccinated against smallpox in the Army during 1942–45. The medical histories of eight cases of postvaccinal encephalitis reported for 1942–45<sup>16</sup> were examined by this author. The diagnosis appeared doubtful in four of these because the interval between vaccination and onset of nervous symptoms was either as short as 2 to 3 days or as long as 31 days. Two of the four doubtful cases were fatal; the pathologic diagnosis in one was infective polyneuritis, and no specimens were submitted in the other. In the remaining four cases, the history was compatible with the syndrome of postvaccinal encephalitis, the intervals between vaccination and onset of nervous symptoms being 7, 10, 10, and 17 days, respectively. One of this group of four patients died within 24 hours after onset, and detailed post mortem studies were carried out.<sup>17</sup> Although only perivascular infiltration was present without demyelination, the pathologic changes in the nervous system were not incompatible with the diagnosis of postvaccinal encephalitis. Of the three surviving patients, one recovered completely, one had some residual loss of vision, and one was said to have recovered only partially. Subsequently, the Medical Statistics Division, Office of The Surgeon General, U.S. Army, listed 17 admissions for postvaccinal encephalitis or encephalomyelitis in the total Army for the period of 1944–45 (table 6), but this author did not have an opportunity to study the records of these cases.

<sup>14</sup> Letter, Lt. Col. A. B. Sabin, MC, to Preventive Medicine Service, Office of the Surgeon General, attn: Brig. Gen. S. Bayne-Jones, 18 Jan. 1946, subject: Positive Serological Tests for Japanese B Encephalitis Virus With Sera From Cases of Encephalitis in Military Personnel in the Philippines (July–August 1945).

<sup>15</sup> Salafranca, E. S., and Espiritu, L.: Report on the Presence of Japanese B Encephalitis Neutralizing Antibody Among Filipinos and Certain Philippine Animals. *Am. J. Trop. Med.* 29: 219–227, March 1949.

<sup>16</sup> Letter, Lt. Col. A. P. Long, MC, Chief, Infectious Disease Control Branch, Office of the Surgeon General, to Dr. W. G. Workman, Division of Biologics Control, National Institute of Health, U.S. Public Health Service, Bethesda, Md., 28 May 1947.

<sup>17</sup> Report, A. B. Sabin, M.D., to the Commission on Neurotropic Virus Diseases, Army Epidemiological Board, 27 Apr. 1942, subject: Case of Postvaccinal Encephalitis in a Soldier at Fort Thomas, Ky.

TABLE 6.—*Admissions for postvaccinal encephalitis (including postraccinal encephalomyelitis) in the U.S. Army, by theater or area and year, 1942-45*

[Preliminary data based on sample tabulations of individual medical records]  
 [Rate expressed as number per annum per 1,000 average strength]

Theater or area	1944-45		1944		1945	
	Number	Rate	Number	Rate	Number	Rate
Continental United States-----	1	0. 00	1	0. 00	-----	0. 00
Overseas:						
Mediterranean <sup>1</sup> -----	5	0. 00	0		5	0. 01
Pacific Ocean Area-----	6	0. 00	6	. 01	-----	0
Southwest Pacific-----	5	0. 00	0		5	0. 00
Other theaters-----	0		0		-----	0
Total overseas-----	16	0. 00	6	0. 00	10	0. 00
Total Army-----	17	0. 00	7	0. 00	10	0. 00

<sup>1</sup> Includes North Africa.

NOTE.—The strengths on which the rates were based are mean strengths and will vary therefore from the official strength reports of The Adjutant General.

Absolute zero is indicated by zero in the units column; 0.0 indicates a rate of more than zero but less than 0.05 and 0.00 a rate of more than zero but less than 0.005.

### Research Under Army Auspices

Extensive investigations were carried out during the war years on the epidemiology of the arthropodborne virus encephalitides and on the development and evaluation of vaccines for human use. The work of Hammon and Reeves at the George Williams Hooper Foundation of the University of California on western equine and St. Louis encephalitis established the importance of various mammalian, avian, and insect hosts in the natural history of these viruses and incriminated *Culex tarsalis*, and probably also *Culex pipiens*, as the most important mosquito vectors during epidemics and epizootics of these diseases.<sup>18</sup> The same investigators also demonstrated the ability of seven species (three genera) of California mosquitoes to transmit the virus of Japanese B encephalitis under experimental conditions.<sup>19</sup> The first American field investigations on Japanese B encephalitis on Okinawa in 1945 also brought to light the importance of various mammalian domestic animals in the natural

<sup>18</sup> Hammon, W. McD., and Reeves, W. C.: Recent Advances in the Epidemiology of the Arthropodborne Virus Encephalitides; Including Certain Exotic Types. *Am. J. Pub. Health* 35: 994-1004, October 1945.

<sup>19</sup> Reeves, W. C., and Hammon, W. McD.: Laboratory Transmission of Japanese B Encephalitis Virus by Seven Species (Three Genera) of North American Mosquitoes. *J. Exper. Med.* 83: 185-194, March 1946.

history of this virus and suggested that domestic fowl probably were not implicated in the infection chain.<sup>20</sup>

Although large-scale vaccination of horses against both eastern and western equine encephalitis had been used successfully in the United States since 1935, human vaccination against these virus infections had been practiced on a limited scale before 1942, chiefly among laboratory workers. Following the first extensive epidemic of western equine encephalitis in 1941 in Northwestern United States and in Canada, approximately 3,000 Canadian farmers were vaccinated in 1942 with formalized chick embryo vaccine prepared by the Lederle Company. Through the cooperation of Drs. F. W. Jackson and C. R. Donovan of the Province of Manitoba, members of the Commission on Neurotropic Virus Diseases of the Army Epidemiological Board were enabled to determine the incidence, speed, and persistence of the antibody response. Tests<sup>21</sup> for neutralizing antibody indicated that while a single dose of 1 cc. of the vaccine used was effective in stimulating a significant antibody response in 7 percent (of 30 persons) at the end of 1 week and in 70 percent (of 13 persons) at the end of 2 weeks, two doses of 1 cc., 1 week apart, produced a 100-percent response in 17 persons at the end of 2 weeks, which persisted for 4 months in 81 percent of 16 persons tested. Seven of the persons who were positive at 4 months were still positive at the end of 1 year in tests performed by Olitsky, Morgan, and Schlesinger.<sup>22</sup> Complement fixation tests carried out by Dr. J. Casals<sup>23</sup> on the 2-week, 4-month, and 1-year specimens of the same seven persons were, however, all negative. During an outbreak of western equine encephalitis in Kern County, Calif., in 1943, Ward<sup>24</sup> vaccinated 280 of a group of 575 Mexican agricultural workers, but no cases of the disease developed in either the vaccinated or the unvaccinated group.

The design of research on vaccines for St. Louis and Japanese B encephalitis was influenced by the fact that they would be used in the face of epidemics which run their course in a few weeks. Accordingly, it was necessary that the vaccines be capable of conferring protection rapidly, that is within at least 1 week rather than after a series of many doses over a period of many weeks, and that they should retain the desired potency after storage for long periods of time. These objectives were achieved, at least so far as it was possible to

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<sup>20</sup> (1) See footnote 8, p. 13. (2) As the result of extensive investigations of the ecology of Japanese encephalitis in Japan, conducted during the period 1955-59, Scherer and Buescher came to the conclusion that the primary, if not the sole, mosquito vector was *Culex tritaeniorhynchus*, and that in the virus-cycle multiple hosts were involved—"the wild avian and porcine amplifying hosts" in addition to man. See Scherer, W. F., Buescher, E. L., et al.: (series of nine papers) *Am. J. Trop. Med. & Hyg.* 8: 645-722, November 1959.

<sup>21</sup> Reports, A. B. Sabin and R. Ward, to Commission on Neurotropic Virus Diseases, Army Epidemiological Board, dated 1 Aug. 1942 and 4 Apr. 1943, subject: Results of Neutralization Tests Before and After Vaccination of Human Beings (Canada) With Western Equine Encephalomyelitis Chick Embryo Vaccine (Lederle).

<sup>22</sup> Preliminary Report, P. K. Olitsky, I. M. Morgan, and R. W. Schlesinger, to the Commission on Neurotropic Virus Diseases, Army Epidemiological Board, 21 June 1943, subject: Follow-up Study of the 1942 Canadian Vaccination Series.

<sup>23</sup> See footnote 22.

<sup>24</sup> Reports, Robert Ward, M.D., to Commission on Neurotropic Virus Diseases, Army Epidemiological Board, 5 Aug. 1943 and 23 Jan. 1944, subject: Vaccination of Mexican Agriculture Workers Against Western Equine Encephalomyelitis in Kern County, Calif.



determine in tests on mice under defined, experimental conditions.<sup>25</sup> Success depended on the selection of (1) the best strain of virus, (2) the host in which maximal propagation was obtained, (3) the most suitable procedure of destroying infectivity of the virus without loss of antigenicity, and (4) the most suitable procedure for assaying antigenic potency. It also depended on the discovery that preservation of antigenic potency on storage could be achieved either by special concentrations of formalin or by lyophilization under defined conditions.

Although it proved possible to produce resistance in mice within 1 week by two doses of vaccine, many of the mice had no neutralizing antibody at this stage, and tests on human volunteers indicated that antibody did not appear before 2 weeks after inoculation.<sup>26</sup> Nevertheless, the assay method, which was finally selected for the Japanese B encephalitis vaccines, produced on a large scale for use by the Army, measured the minimal amount of vaccine which was capable of protecting mice within 1 week after the first inoculation. Although satisfactory lyophilized vaccines could be prepared when the work was done on a small laboratory scale, pilot tests by Sharp & Dohme, Inc., by the methods employed commercially in 1943, yielded products which were largely denatured and practically without antigenic potency. Accordingly, the Japanese B encephalitis vaccine which was finally prepared on a large scale for the Armed Forces consisted of 10 percent uncentrifuged mouse brain suspension in physiologic salt solution in which the virus was inactivated by 0.2 percent formalin at 2° to 5° C., the final product being stored and shipped in the fluid state in the cold. Preliminary tests of such a vaccine, possessing on mouse assay a 50-percent immunogenic dose of 0.0055 cc., administered in 2 doses, 2 cc. each, 3 days apart, to the personnel of the commercial laboratories engaged in the large-scale production of this vaccine, indicated that, at 2 weeks after inoculation, 52 percent of 25 persons, aged from 18 to 35 years, developed significant titers of neutralizing antibody.<sup>27</sup> This provided the basis for the manner in which the vaccine was subsequently used on a large scale in military personnel on Okinawa.<sup>28</sup>

## SUMMARY AND EVALUATION OF EXPERIENCE

The terms "encephalitis" and "encephalomyelitis" were used without qualification for a variety of unrelated clinical and epidemiologic entities, and no reliable statistics are available on the relative incidence of the various

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<sup>25</sup> Sabin, A. B., Duffy, C. E., Warren, J., Ward, R., Peck, J. L., Jr., and Ruchman, I.: The St. Louis and Japanese B Types of Epidemic Encephalitis; Development of Noninfective Vaccines: Report of Basic Data. *J.A.M.A.* 122: 477-486, June 1943.

<sup>26</sup> Sabin, A. B., and Duffy, C. E.: Antibody Response of Human Beings to Centrifuged, Lyophilized Japanese B Encephalitis Vaccine. *Proc. Soc. Exper. Biol. & Med.* 65: 123-126, May 1947.

<sup>27</sup> Sabin, A. B.: Antibody Response of People of Different Ages to Two Doses of Uncentrifuged, Japanese B Encephalitis Vaccine. *Proc. Soc. Exper. Biol. & Med.* 65: 127-130, May 1947.

<sup>28</sup> (1) See footnote 8, p. 13. (2) For an official description and discussion of the Japanese B encephalitis vaccine see Long, Arthur P.: The Army Immunization Program. In Medical Department, United States Army. Preventive Medicine in World War II. Volume III. Personal Health Measures and Immunization. Washington: U.S. Government Printing Office, 1955, pp. 327-331.



forms. An examination of large numbers of clinical records suggests, however, that the vast majority of the "hundreds" of cases of encephalitis reported between 1940 and 1945, chiefly in the United States, were instances of toxic encephalopathy associated with various bacterial infections or occurred in association with mumps, measles, German measles, or chickenpox. Although a group of 12 cases of mild encephalitis of unidentified etiology, but possibly due to an arthropodborne virus, occurred during maneuvers in Texas in 1941, no other epidemic of viral encephalitis occurred among the Armed Forces in the United States. The only identified outbreak of encephalitis occurred on Okinawa in 1945, where 11 unequivocal cases of Japanese B encephalitis were confirmed by laboratory methods, although a total of 38 cases with various clinical manifestations referable to the nervous system were investigated. Similar small outbreaks of encephalitis occurred in 1945 among American forces in China and in the Philippine Islands, and although they were either not investigated or incompletely studied by laboratory methods the possibility exists that these were also due to the virus of Japanese B encephalitis.

The lessons learned on Okinawa regarding the potential threat to a military force of an epidemic of encephalitis due to the Japanese B encephalitis virus were as follows:

1. The incidence of the disease among susceptible military personnel located close to a focus of infection is unpredictable but can be very small.
2. The disease did not occur among military personnel stationed at a distance of many miles from the native population and their domestic animals.
3. Vaccination of a large force in the field is so time consuming a task that one may expect to gain very little from it when it is started once an epidemic is well established.
4. The pressure of moral and other considerations is so great during an epidemic, whose ultimate course is unpredictable, that when a vaccine of potential though unproved value is available, it is good policy to be prepared to use it intelligently.

Research carried out under the auspices of the Preventive Medicine Service during World War II led to a better understanding, although only partial elucidation, of the natural history of the arthropodborne viral encephalitides and to the development of vaccines for Japanese B and St. Louis encephalitis suitable for field trial in case of need.



## CHAPTER III

# Bartonellosis

*Marshall Hertig, Ph. D.*

Bartonellosis is a specific infectious disease, at times fatal, caused by *Bartonella bacilliformis* and transmitted by the bite of *Phlebotomus*. The disease is limited to certain parts of Peru, Ecuador, and Colombia. The disease was not a military problem in World War II. American troops stationed in Peru (Talara) and Ecuador (Salinas) were outside the endemic areas. However, since some of the experimental work on protective measures and control of sandflies and sandflyborne diseases was done in the Peruvian verruga zone, an account of the disease and its setting may be appropriately included in this history.

## HISTORICAL NOTE

Bartonellosis sprang into prominence in the 1870's when the railroad from Lima to Oroya was being built.<sup>1</sup> After the construction reached elevations above 1,000 meters and 45 or 50 kilometers inland from Lima, there were a great many fatal cases of what was apparently a new disease. Of some 7,000 deaths among the workmen, from all causes, the majority were thought to be from the new disease, which received its name, Oroya fever, from the railroad's projected terminus. There began a controversy in medical circles as to whether or not Oroya fever had any relation to the well-known verruga, a relatively mild eruptive disease endemic in the same region. The name Carrión's disease, applied to both types, was derived from the classic experiment of Carrión, a medical student, who in 1885 inoculated himself from an eruptive case and died apparently with the anemic form of the disease. The controversy was finally settled only with the cultivation of the etiologic agent by Noguchi and Battistini,<sup>2</sup> in 1926, which provided the clinching evidence that the two chief clinical syndromes, which differ so remarkably, are actually manifestations of one and the same disease.

## ANEMIC AND ERUPTIVE FORMS OF BARTONELLOSIS

### Symptomatology

The anemic form of the disease (Oroya fever) has an incubation period of about 3 weeks. The onset, with irregular fever and general malaise, is followed

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<sup>1</sup> For a historical summary see Hertig, M.: *Phlebotomus* and Carrión's Disease. *Am. J. Trop. Med.* 22 (Suppl.): 1-80, July 1942.

<sup>2</sup> Noguchi, H., and Battistini, T. S.: Etiology of Oroya Fever. I. Cultivation of *Bartonella bacilliformis*. *J. Exper. Med.* 43: 851-864, June 1926.

by a rapidly developing profound anemia, accompanied at times by pains in bones and joints.<sup>3</sup> The mortality of this form of the disease varies from 20 to 70 percent. During the anemic phase, the minute rodlike, coccoid, and filamentous forms of *B. bacilliformis* may be found, often in great numbers, in or on the red cells. If the patient survives, there usually follows, after a variable interval, the typical eruption.

The eruptive form (*verruca peruana*) usually has no marked anemic phase. This benign type of the disease includes by far the largest proportion of the total number of infections. The incubation period is variable and may be as much as a month or two. The onset is characterized by bone and joint pains, irregular fever, and malaise. Sooner or later, at times after months, during which there may have been remission of the symptoms, the eruption appears, with or without the initial symptoms. The eruption takes the form of hemangioma-like nodules, commonly from 2 to 3 mm. in diameter but varying from minute points to raised nodules of 10 or 20 mm. in diameter, which give the disease its name, *verruca* (Spanish for wart). The nodules are distributed chiefly on the extremities and face and vary in number from few to thousands. They are not painful. The eruption usually lasts a month or two and finally heals without leaving scars.

### Proportion of Severe Anemic to Eruptive Cases

The evidence is rather unsatisfactory as to the proportion of total infections which develop the severe anemia. It appears that it may vary in different places and at different times. In any case, the anemic form has been rare among natives of the *verruca* zone in Peru in recent years. Most of the anemic cases have been in adults, who, without previous exposure to the disease, were engaged in construction work, exploration, or guard duty. During the early history of the disease in Peru, the proportion of severe anemia and the mortality must have been very high, to judge from the great number of fatal cases that occurred during the railroad construction and from the separate accounts of 10 to 75 percent of the specific groups dying from the disease.<sup>4</sup> (The mortality in the Colombian epidemic (see p. 27) was also very high.) However, during the author's stay in Peru, 1937-42, the proportion of anemic cases was distinctly low. The author was able to follow more or less closely the fate of guards stationed at railroad bridges in the Rimac Valley *verruca* zone during the war.<sup>5</sup> About three-fourths of the nonimmune persons contracted the disease during a 1-month tour of duty. When the tour was extended, about nine-tenths acquired the infection within 4 months. About 150 men, immune and nonimmune, were involved, with about 100 cases among them, only 4 of which were fatal. During this same period before any control method was known, there were

<sup>3</sup> For a clinical account, see Strong, Richard P.: *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*. 7th edition. Philadelphia: The Blakiston Co., 1944, vol. II, pp. 997-1014.

<sup>4</sup> See footnote 3.

<sup>5</sup> Howe, C., and Hertig, M.: *Prophylactic Immunization Against Carrión's Disease*. *J. Immunol.* 47: 471-482, December 1943.



several large construction projects with many workmen, but there were only scattered cases of the severe anemic form.

### Vaccination

A detachment of 22 nonimmune bridge guards, not included in the aforementioned totals, was inoculated with formalized suspension of *B. bacilliformis*.<sup>6</sup> While slightly over one-half the guards became infected during the 7 months they were under observation, the clinical course was remarkably mild. It was concluded that vaccination might be of value in ameliorating the course of this potentially serious disease.

### Therapy

There is no specific therapy. In a recent visit to Peru, the author was informed that results with the newer antibiotics were conflicting. In the treatment of the severe anemic cases, massive blood transfusions have at times been valuable.<sup>7</sup>

### Immunity

The immunity from a single attack is considerable but not solid. Repeated attacks are known but usually run a mild clinical course. Natives of the verruga zone usually acquire the disease as mild childhood infections and in general do not regard the disease seriously. In certain surveys, about 10 percent of the local population have been shown to harbor *B. bacilliformis*, with or without a previous history of the disease.<sup>8</sup>

### Etiology

*B. bacilliformis*, of uncertain systematic position, is probably related to the bacteria. It is a minute, gram-negative micro-organism comparable in size and general appearance to the rickettsiae, with rodlike, coccoid, and filamentous forms. It is cultivable in Noguchi's semisolid medium and its later modifications. Subcultures, but not primary isolations, are successful on ordinary blood agar. The organism is at times motile by means of a terminal tuft of flagella. *Bartonella* may usually be recovered in culture from the blood at any stage of any clinical form of the disease and also from the nodules.

## EXPERIMENTAL INFECTIONS

Monkeys are the only animals known which can be readily infected. Intradermal injections of cultures or tissue from nodules give rise to typical nodules at the sites of inoculation, which, however, is ordinarily not the case with *Bartonella* from other sources, for reasons not understood. The inocula-

<sup>6</sup> See footnote 5, p. 24.

<sup>7</sup> Hodgson, C. H.: The Treatment of Carrión's Disease With Large Transfusions. *Am. J. Trop. Med.* 27: 69-72, January 1947.

<sup>8</sup> Weinman, D., and Pinkerton, H.: Carrión's Disease. IV. Natural Sources of *Bartonella* in the Endemic Zone. *Proc. Soc. Exper. Biol. & Med.* 37: 596-598, December 1937.

tion of blood or tissues from an anemic patient, or suspensions of sandflies, or infective bites of sandflies, produce infection in Rhesus monkeys, which is demonstrable by blood culture but without any external sign. The anemic form of the disease is extremely rare in experimental infections. A single specimen of field mouse has been found naturally infected, but attempts to infect this specimen and other rodents in the laboratory failed.<sup>9</sup>

## TRANSMISSION

For many years, it was thought that the disease came from drinking water of the endemic area, but with the realization about 1909 that the disease was contracted only at night, attention was immediately directed to insects as vectors. Townsend, in 1913, first discovered the presence of *Phlebotomus* in Peru and showed that the distribution of *Phlebotomus verrucarum* was correlated with that of the disease.<sup>10</sup> Noguchi<sup>11</sup> and his associates showed that sandflies of the verruga zone harbored the etiologic agent. The author<sup>12</sup> was able to transmit the infection to Rhesus monkeys by the bites of wild-caught *P. verrucarum*.

*P. verrucarum* is the principal and perhaps the sole vector. Only one other species, *Phlebotomus noguchi*, is found throughout the verruga zone, and it does not feed on man. *Phlebotomus peruensis* is limited to the upper half of the verruga zone, and *Warileya phlebotomanica*, a close relative of *Phlebotomus*, is rare.

There are still a number of unsolved phases of the transmission problem. The source of the sandfly infection is unknown. From the readiness with which the infection may be acquired in certain areas which are all but uninhabited the reservoir is probably other than man. There has been mentioned the instance of a naturally infected field mouse, but the failure to infect this and other animals leaves the question open. No cycle of development of *Bartonella* in the sandfly has been demonstrated. Certain massive infections of the tip of the proboscis with various micro-organisms of unknown origin may eventually be shown to have some bearing on the source of the *Bartonella* infection. The great majority of the proboscis infections are caused by a cultivable, unidentified micro-organism, but *B. bacilliformis* has been isolated twice in cultures from such infected proboscides.<sup>13</sup>

It may be remarked that in the Peruvian verruga zone cutaneous leishmaniasis also occurs, but its distribution by no means coincides with that of bartonellosis. It is limited to the upper part of the verruga zone, though it also occurs in other parts of Peru where there is neither verruga nor *P. verrucarum*, but where there are other species of *Phlebotomus*.

<sup>9</sup> See footnote 1, p. 23.

<sup>10</sup> See footnote 1, p. 23.

<sup>11</sup> Noguchi, H., Shannon, R. C., Tilden, E. B., and Tyler, J. R.: Etiology of Oroya Fever, XIV. The Insect Vectors of Carrión's Disease. J. Exper. Med. 49:993-1108, June 1929.

<sup>12</sup> See footnote 1, p. 23.

<sup>13</sup> See footnote 1, p. 23.

The life history of *P. verrucarum* is essentially similar to that of *Phlebotomus papatasi*, described in chapter IX, p. 113. Breeding is continuous throughout the year and there is no diapause. (Bartonellosis is likewise contracted at any time of the year.) Breeding places are chiefly in rock crevices and under boulders or stone walls. The vegetation of the verruga zone is scanty, and there are few large trees. Diurnal shelters include the breeding places, together with caves and houses, which the sandflies enter freely. They are active from dusk to early morning, and only rarely do they bite by day.

The nocturnal habit of the sandfly has been taken advantage of in one very effective method of preventing the disease which has been practiced for 40 years by the Central Railroad of Peru. Construction crews are removed in special work-trains every afternoon to a town below the verruga zone and taken back in the morning.

### DISTRIBUTION

In Peru, the disease is limited chiefly to the Pacific slope of the Andes between 6° north and 13° south and at altitudes between 800 and 3,000 meters above sea level. The most intense foci and those which have been best studied are in the valley of the Rimac River and its tributary, the Santa Eulalia, and in the Callejon de Huaylas, a portion of the valley of the Santa River in the Department of Ancash. *P. verrucarum* is found throughout the Peruvian verruga zones, as far as studies have gone, and has not been found elsewhere in Peru or in other countries.

In Ecuador, bartonellosis has been reported from the Provinces of Loja and Oro. This author<sup>14</sup> cultivated *B. bacilliformis* from a blood specimen sent to Lima from the latter Province. There is very little recorded information about the incidence of the disease in Ecuador and none whatever about *Phlebotomus* in the endemic region.

Early in 1936, in Colombia in the Department of Nariño near the Ecuadorian border, an epidemic broke out which caused an estimated 4,000 deaths in a district with a population of 100,000. The disease was finally diagnosed as bartonellosis.<sup>15</sup> The severe anemic form apparently predominated. It was thought to be a newly introduced disease. The author visited this region in 1945.<sup>16</sup> By that time, the epidemic had apparently died out completely in those places where it had first appeared. The only known focus, which unfortunately could not be visited, was represented by a very few cases at the northern edge of the area which the disease had reached. Three years previously, sandflies, mostly *Phlebotomus colombianus* (a species very closely related to *P. verrucarum*), had been very abundant in several towns, as witnessed by collections, examined by this author, which had been made by Colombian investigators. In 1945, the author, in company with Colombians who had

<sup>14</sup> Hertig, M.: Cultivo de la *Bartonella bacilliformis* de un caso de verruga en El Ecuador. Bol. Ofic. San. Panamer. 19: 756-758, August 1940.

<sup>15</sup> Patiño, C. L.: Un nuevo foco de bartonellosis en América. Bol. Ofic. San Panamer. 18: 305-313, 1939.

<sup>16</sup> Annual Report of The Gorgas Memorial Laboratory, 1945.



taken part in the previous studies, made collections in a number of the same places, during the same month of the year, and by the same methods (mostly with horses as bait)—sandflies were extremely scarce. Whereas in 1942, catches often consisted of a hundred or more sandflies, in 1945 only scattered specimens, often none at all, were obtained. Clearly something had happened to the sandflies. It is to be regretted that this epidemic, which bore every appearance of a new introduction, came and went without adequate entomologic studies throughout its course.

### PROTECTIVE AND CONTROL MEASURES

Studies on repellants and control with DDT were undertaken during the war by Dr. G. B. Fairchild and this author<sup>17</sup> in the Rimac Valley near Lima (fig. 1) and are summarized in chapter IX (p. 125). This area was chosen because sandflies attacking man were abundant in a region easily accessible and intimately known to the author. Many species of *Phlebotomus* are so similar in the essentials of their life history and in their flight and feeding habits, especially those species which enter houses and bite man, that it seemed likely that results obtained in control studies with one species might readily be applied to the control of other species. This has proved to be the case. Residual DDT has been shown to be extremely effective in the control of *Phlebotomus* wherever it has been tried.



FIGURE 1.—Loose-laid stone boundary walls, a frequent source of the *Phlebotomus*, in the vicinity of a dwelling.

<sup>17</sup> Hertig, M., and Fairchild, G. B.: The Control of *Phlebotomus* in Peru With DDT. *Am. J. Trop. Med.* 28 : 207-230, March 1948.



## CHAPTER IV

# Dengue

*Oliver R. McCoy, M.D., and Albert B. Sabin, M.D.*

### Part I. Epidemiologic Considerations

*Oliver R. McCoy, M.D.*

Although dengue is a nonfatal disease and seldom lasts more than 5 to 7 days, it sometimes assumed considerable military importance in World War II because of its tendency to occur in epidemics which resulted in the sudden incapacitation of large numbers of men. This was particularly true when nonimmune forces occupied territory in an endemic area where control of the mosquito vector had become lax and protective measures for personnel were not enforced. Conditions during and immediately following combat frequently favored mosquito breeding and the spread of dengue. The disease was a hazard throughout the war in practically all areas of the Pacific and Asiatic theaters.

The incidence of dengue in the U.S. Army during World War II, according to theaters of operations, is shown in table 7. A few scattered cases were reported in the European, Latin American, Mediterranean, and Africa-Middle East theaters, and also in the continental United States. Although dengue is known to occur in these regions, the question may be raised as to the validity of the diagnosis in isolated cases because of the lack of means for specific diagnosis. On the other hand, failure to recognize dengue and difficulty in diagnosis may have resulted in the reporting of cases as fever of undetermined origin. In the absence of an epidemic, this was undoubtedly true even in theaters where the disease was prevalent.

The epidemic characteristics of dengue are well illustrated in the curve of reported incidence, by months for the years 1942 through 1945, in the U.S. Army overseas (chart 1). Although seasonal factors are influential to a certain extent, the peak rates are due chiefly to sharp outbreaks which occurred under specially favoring circumstances in fairly localized areas. It is notable that the dengue rate remained low throughout the year 1945 even though large numbers of men, including nonimmune reinforcements, continued military operations in endemic areas. This may be explained by the fact that efficiency in mosquito control was vastly improved during the last year of the war.

TABLE 7.—Incidence of dengue in the U.S. Army, by theater and year, 1942-45

[Preliminary data based on sample tabulations of individual medical records]  
[Rate expressed as number of cases per annum per 1,000 average strength]

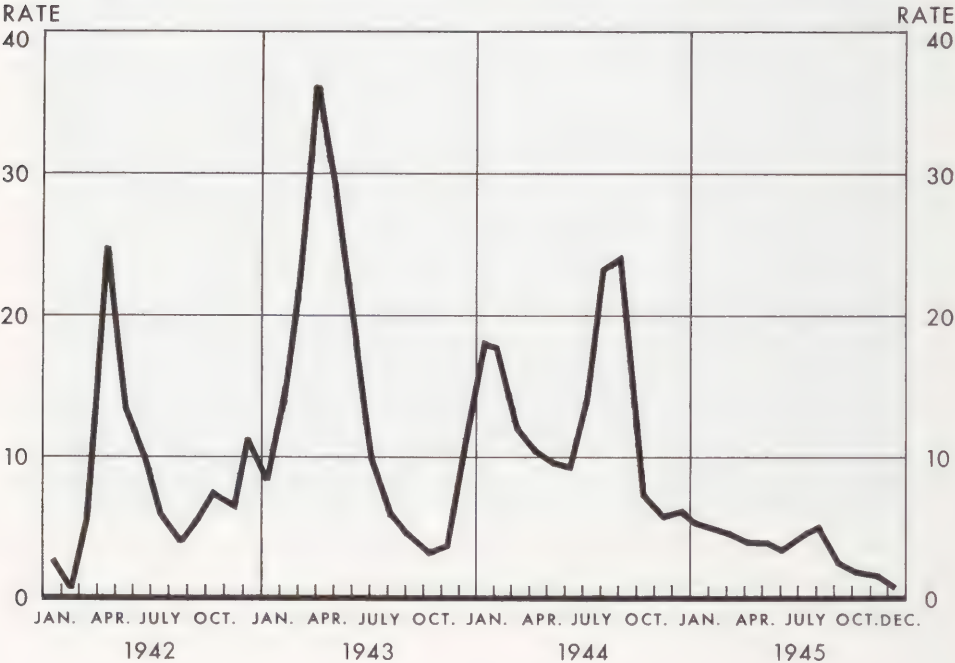
Theater or area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States -----	75	0.01	6	0.00	25	0.00	19	0.00	25	0.01
Overseas:										
Europe -----	91	0.02	1	0.01	0		35	0.02	55	0.03
Mediterranean <sup>1</sup> -----	358	.23	1	.04	84	.18	213	.33	60	.15
Middle East -----	35	.26	1	.17	24	.45	10	.22		0.00
China-Burma-India -----	8,217	18.37	73	8.35	999	25.22	5,240	31.06	1,905	8.27
Southwest Pacific -----	50,903	32.10	4,225	59.32	6,436	33.89	28,292	52.47	11,950	15.21
Central and South Pacific -----	29,941	20.79	19	.13	11,650	39.96	16,442	37.48	1,830	3.27
North America <sup>2</sup> -----	3	.01		0	3	.02	0			0
Latin America -----	245	.64	120	1.18	49	.41	46	.54	30	.42
Transports -----	993		2		60		826		105	
Total overseas <sup>3</sup> -----	90,786	8.61	4,442	7.58	19,305	11.44	51,104	13.38	15,935	3.58
Total Army -----	90,861	3.59	4,448	1.37	19,330	2.81	51,123	6.56	15,960	2.15

<sup>1</sup> Includes North Africa.  
<sup>2</sup> Includes Alaska and Iceland.  
<sup>3</sup> Includes rate for transports.

NOTE.—The use of 0.00 indicates a rate of less than 0.005.

CHART 1.—Incidence rates for dengue in the U.S. Army overseas, by month and year, January 1942 to December 1945

[Rate expressed as number of admissions per annum per 1,000 average strength]



## VECTORS

Before the war, *Aedes aegypti* and *Aedes albopictus* were the only proved vectors of dengue. Since *A. aegypti* had practically universal distribution in the Tropics, it was generally accepted as the probable vector in regions where the epidemiology of the disease had not been studied. However, *A. albopictus* was known to be an efficient vector in the Philippines, Formosa, and Sumatra,<sup>1</sup> and proved to be an important vector in the outbreak of dengue which occurred in Hawaii in 1943.<sup>2</sup> There, *A. albopictus* was found not only in populated areas, in places typically chosen by *A. aegypti* (tin cans, flower pots, bottles, tires, tanks, and the like), but also in forested regions as high as 2,000 feet above sea level, where it was found breeding in tree holes and in water collections at the bases of plant leaves. *A. albopictus* also was abundant during the dengue epidemic which occurred on Saipan in August and September 1944.<sup>3</sup>

During an outbreak of dengue in the New Hebrides early in 1943, *Aedes scutellaris hebrideus* Edwards was suspected as a vector.<sup>4</sup> *A. scutellaris* (probably in the form of the typical subspecies) also was suspected to be a main vector of dengue in New Guinea, since *A. aegypti* was rare or absent in areas where the disease was prevalent.<sup>5</sup> The suitability of *A. scutellaris* as a vector of dengue was proved by Australian workers. In these experiments, specimens of this and three other local species were allowed to feed on dengue patients in the Finschhafen area of New Guinea. The mosquitoes were then shipped by air to Sydney, Australia, which is outside the dengue zone, and there were fed on volunteers who had never been in a dengue area. Typical cases of the disease occurred in three men on whom *A. scutellaris* were fed, but not in those bitten by specimens of the other three species, *Aedes auremargo*, *Armigeres breinli*, and *Armigeres milnensis*.

*A. scutellaris*, in common with most of the members of the subgenus *Stegomyia* (that is, *A. aegypti* and *A. albopictus*), breeds almost exclusively in what are known as artificial water containers (as opposed to ground pools). In New Guinea, the larvae were found in a wide variety of such places, including tree holes, rot holes in fallen logs, tin cans, metal and wooden barrels, and coconut hulls. They were taken usually in fairly clear water or in water containing leaves and some decaying organic matter, but not in the fermenting liquid in coconut shells from which the meat had not been removed. Also, they were not found in the leaf axils of water-holding plants and rarely in fallen leaves or palm bracts, which are favorite sites for certain other species with more specialized breeding habits.

<sup>1</sup> Strong, Richard P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases. 7th edition. Philadelphia: The Blakiston Co., 1943, vol. II, p. 908.

<sup>2</sup> Usinger, R. L.: Entomological Phases of the Recent Dengue Epidemic in Honolulu. Pub. Health Rep. 59: 423-430, 31 Mar. 1944.

<sup>3</sup> Letter, 217th Medical Composite Unit (Malaria Survey), to Surgeon, Army Ground Forces, 5 Jan. 1945, subject: Mosquito Survey of Saipan.

<sup>4</sup> Daggy, R. H.: *Aedes scutellaris hebrideus* Edwards. A Probable Vector of Dengue in the New Hebrides. War Med. 5: 292-293, May 1944.

<sup>5</sup> King, W. V.: Notes on the Vectors of Dengue in New Guinea. [Professional paper.]



The adults of *A. scutellaris* appeared to be almost exclusively daytime feeders, but were chiefly active only under conditions of high humidity. They were annoying in quarters, latrines, and showers principally during the early morning and late afternoon, but also were more or less active throughout the day during rainy periods or in dense shade in the jungle. In Hawaii, it was shown that *A. albopictus* was a persistent biter during the day but did not bite at night.

## EPIDEMICS AND CONTROL MEASURES

**Australia.**—An extensive epidemic of dengue occurred among U.S. Army troops stationed in Northern Territory and Queensland in March, April, and May, 1942. Approximately 80 percent of all U.S. personnel in this area were attacked within a period of about 3 months.<sup>6</sup> Epidemics also occurred among U.S. troops in the following year in January, February, and March—one at Rockhampton and one in the Brisbane area.<sup>7</sup> The peak of the epidemic at Rockhampton was reached during the week ending on 6 February 1943 when 94 patients were hospitalized. A total of 463 cases occurred among U.S. military personnel in the vicinity from January through March. A survey of Rockhampton during this period showed that 80 percent of more than 6,000 dwellings examined were breeding dengue-carrying mosquitoes.<sup>8</sup> Labor furnished for mosquito control work by the U.S. Army varied from 15 to 55 men; oil was supplied by the Rockhampton City Council. The city council was asked to assume responsibility for mosquito control, because it was necessary to use the soldiers for military duties, but only four civilians were employed in June 1943. The vector in Australia was *A. aegypti*.

**New Hebrides.**—An epidemic of dengue began at Espíritu Santo early in February 1943, reached its peak in April, and ended in August. During this period, approximately 25 percent of the base strength, or over 5,000 military personnel, were affected.<sup>9</sup> The Army rates per 1,000 per annum are shown in table 8. For several months before the onset of the dengue epidemic, there had been widespread dumping of tin cans over the base without regard to sanitary regulations. This had resulted in heavy breeding of *A. aegypti* and *A. scutellaris hebrideus*. In February 1943, the malaria control unit at the base prepared a directive which listed the various breeding places of *Aedes* mosquitoes and the control measures to be employed. The epidemic continued into June with only slight abatement. A complete mosquito survey was then made of all camp areas, including territory within a radius of 500 yards from the camp. All tin can dumps and collections of water in stored tires, oil drums,

<sup>6</sup> Letter, Chief Surgeon, Headquarters, U.S. Army Services of Supply, Southwest Pacific Area, to The Surgeon General, 15 Dec. 1942, subject: Medical Service in Australia. Inclosure thereto.

<sup>7</sup> Quarterly Report, Base Surgeon, Headquarters Base Section Three, U.S. Army Services of Supply, dated 15 Nov. 1943, for period 1 July–30 Sept. 1943.

<sup>8</sup> Quarterly Report, Surgeon, Headquarters I Corps, U.S. Army, dated 22 June 1943, for period 1 January–31 March 1943.

<sup>9</sup> Malaria News Letter No. 3, Headquarters Malaria and Epidemic Control, South Pacific Area. September 1943.





FIGURE 2.—*Aedes* control. Spraying larvicide in water barrels, Espiritu Santo, New Hebrides, October 1943.

machinery, tarpaulins, and other containers were spotted on maps. An organized cleanup campaign was instituted which utilized approximately 300 men and 40 trucks and other heavy equipment.<sup>10</sup> By August, the epidemic was under control (figs. 2 and 3). Very few cases of dengue occurred at the base during the succeeding rainy season in 1944.

The epidemic at New Caledonia during 1943 was less severe than that at Espiritu Santo. The peak was reached during April (table 8). The wide distribution of breeding places for *A. aegypti* and the lack of preventive measures by the resident population contributed to the persistence of the disease.<sup>11</sup> Intensive mosquito control measures instituted by the base malaria control unit greatly reduced the incidence in military personnel, and although a considerable number of cases occurred at the base during the 1944 rainy season, no epidemic developed.

<sup>10</sup> See footnote 9, p. 32.

<sup>11</sup> Stevens, F. W.: History of Medicine, South Pacific Area. [Official record.]



FIGURE 3.—*Aedes* control. Introducing larva-eating gambusia into water tank, Espiritu Santo, New Hebrides, October 1943.

TABLE 8.—Incidence rates for dengue in U.S. Army personnel in New Caledonia and Espiritu Santo, January to August, 1943 and 1944

[Rate expressed as number of cases per annum per 1,000 average strength]

Month	New Caledonia		Espiritu Santo	
	1943	1944	1943	1944
January.....	0. 0	1	-----	1
February.....	65	15	441	1
March.....	186	120	1, 095	0. 0
April.....	645	56	1, 713	0
May.....	317	16	1, 531	0
June.....	66	5	909	0
July.....	30	1	245	0
August.....	3	1	82	0

Source: Stevens, F. W.: History of Medicine, South Pacific Area. [Official record.]

**Hawaii.**—In 1943, dengue made its appearance in epidemic form in Honolulu, T.H., after an absence of more than 30 years. The disease presumably was imported from the southwestern Pacific region. Two commercial airline pilots were hospitalized with dengue in Honolulu early in July 1943, after arrival from Suva, Fiji Islands, where an epidemic of dengue had been reported. One of the pilots was already ill when he came to Honolulu, but the other had onset of symptoms several days later and was not isolated by hospitalization until he had passed through the infectious period.<sup>12</sup> After 3 weeks, two cases appeared among civilians in the Waikiki area, and 12 days later, two cases occurred in Army personnel in the same section.<sup>13</sup>

Measures were taken immediately to prevent an explosive outbreak. Although 1,355 civilian cases were reported through 31 December 1943, only 56 cases occurred in military personnel. Protective measures consisted chiefly of an extensive mosquito control program. Proper screening of patients in hospitals and in homes was made mandatory, and large areas of the city of Honolulu were placed "off limits" to troops.

Assistance in dengue control was given freely to civilian agencies, because effective control in military establishments was not possible without adequate control in civilian areas. A medical officer was attached to the Territorial Board of Health to make an epidemiologic study of all new cases. Fifty enlisted men were assigned to spray the buildings and eliminate mosquito breeding places in homes in which there were cases of dengue. Trucks, ladders, and spraying equipment were made available for use by civilian agencies.

Extension of the dengue control program to include the entire city of Honolulu became necessary in September 1943. The program was supervised by the U.S. Public Health Service, although most of the labor personnel were soldiers from a medical service company. Honolulu was divided into 3 districts and subdivided into 77 inspection zones, each of such size that one man could thoroughly cover his zone every 10 days.

*Aedes* mosquitoes were found breeding in all sizes and types of containers that would hold water. The usual variety of such receptacles found in the continental United States were observed in Honolulu (tin cans, bottles, barrels, jars, flower vases, ant cups, animal drinking pans, tanks, tubs, tires, storm drains, catch basins, unstocked fish ponds, abandoned cesspools, and a few cisterns). The new breeding places encountered were principally those afforded by the subtropical vegetation, especially water-holding plants such as spider lilies, pineapple lilies, and aloe plants, also, rotted-out holes and crotches in poinciana, algarroba, haole koa and guava trees, bamboo and banana stumps, and the large water-holding pockets in traveler's palms. Other unusual breeding places were found in fallen palm fronds, the holes of lava-formed rocks, and pockets in emerged coral reef formations. In over a million inspections,

<sup>12</sup> Essential Technical Medical Data, Central Pacific Base Command, for October 1944, dated 28 Nov. 1944—Inclosure 8, subject: Sanitary Aspects of the Control of the 1943-44 Epidemic of Dengue Fever in Honolulu.

<sup>13</sup> History of Preventive Medicine, Headquarters, U.S. Army Forces, Middle Pacific. [Official record.]



on only four occasions were ground pools found to be breeding places for *Aedes* mosquitoes. Since both *A. aegypti* and *A. albopictus* have short ranges of flight (up to 200 yards), control operations were extended only to the fringes of the inhabited area. The breeding indexes for *Aedes* in Honolulu during the period of the epidemic are shown in table 9.

TABLE 9.—Breeding index of *Aedes* mosquitoes in Honolulu, T.H., August 1943 to August 1944

Year and month	Index <sup>1</sup>	Year and month	Index <sup>1</sup>
1943		1944	
August.....	5.7	January.....	1.0
September.....	1.7	February.....	1.9
October.....	1.1	March.....	3.5
November.....	.9	April.....	1.8
December.....	1.2	May.....	1.0
		June.....	1.1
		July.....	.7
		August.....	.8

<sup>1</sup> Percentage of premises inspected in which *Aedes* larvae were found.

In summary, control measures employed in Honolulu were (1) citywide inspections at 10-day intervals to eliminate breeding places, (2) selective spraying to kill adult mosquitoes, and (3) education of the residents in how to prevent mosquito breeding on their premises. Breeding indexes of *Aedes* mosquitoes were reduced satisfactorily by this program. From experiences during the epidemic, it was concluded that the critical index, or threshold of importance for dengue, was 3.0 or less, which is considerably lower than the index (5.0) generally accepted as the critical point for yellow fever.<sup>14</sup>

**New Guinea and the Philippines.**—From the beginning of operations in New Guinea, dengue was an important cause of noneffectiveness of troops. Separate statistics for New Guinea and adjacent islands are not available for 1943, but the monthly record of cases and rates during 1944 and 1945 is shown in table 10. In 1944, the incidence of the disease was highest during January and February, months of heavy rainfall and, during the first 6 months of the year, the rate for dengue exceeded that for malaria. Dengue occurred in epidemic proportions in certain units, notably those in the Hollandia and Biak areas. On Biak Island, dengue was reported to have occurred in a 4 to 1 ratio with malaria.<sup>15</sup> The vector of dengue in New Guinea apparently was *A. scutellaris* rather than *A. aegypti*. Because of the greater variety of breeding places, *A. scutellaris* presented a more difficult control problem. The day-biting habits

<sup>14</sup> Soper, F. L., and Wilson, D. B.: Species Eradication; A Practical Goal of Species Reduction in the Control of Mosquito-borne Disease. J. Nat. Malaria Soc. 1: 5-24, 1942.

<sup>15</sup> Quarterly Report, Surgeon, Headquarters I Corps, U.S. Army, dated 4 July 1944, for period 1 April-30 June 1944.



of this species made individual protective measures necessary at all hours, especially in shaded jungle areas.

TABLE 10.—*Incidence of dengue in U.S. Army personnel in New Guinea and adjacent islands, January 1944 to December 1945*

[Rate expressed as number of cases per annum per 1,000 average strength]

Year and month	Number of cases	Rate	Year and month	Number of cases	Rate
1944			1945		
January-----	3, 137	197. 6	January-----	640	24. 6
February-----	2, 849	164. 1	February-----	576	25. 8
March-----	2, 469	90. 6	March-----	597	25. 5
April-----	1, 848	68. 0	April-----	468	30. 5
May-----	1, 970	66. 1	May-----	353	27. 3
June-----	2, 756	61. 2	June-----	208	15. 3
July-----	2, 613	60. 1	July-----	48	6. 9
August-----	1, 571	33. 6	August-----	35	5. 6
September-----	1, 828	30. 5	September-----	12	2. 8
October-----	1, 102	21. 5	October-----	9	2. 7
November-----	935	23. 5	November-----	11	4. 0
December-----	1, 001	23. 2	December-----	3	3. 3
Total-----	24, 079	54. 2	Total-----	2, 960	21. 4

During 1945, dengue rates in New Guinea remained comparatively low, even in the months of heavy rainfall. Both the improved mosquito control and the building up of immunity from the previous year's experience probably contributed to this result.

In peacetime, dengue had always been a problem among Army forces in the Philippines, replacements frequently acquiring the disease within a few months after arrival. Consequently, a serious situation with respect to dengue was anticipated during the campaign of reoccupation, especially in the more densely populated regions during the rainy season. Although the disease occurred rather generally throughout the islands, no outbreaks of epidemic proportions developed. The number of cases and the rates by months after the campaign of reoccupation began are shown in table 11.

Intensive mosquito control measures were carried out by malaria units attached to all forces operating in the Philippines. Area spraying of DDT from airplanes was done extensively over Manila and other populated centers in Luzon during the early months of 1945.<sup>16</sup> Also, a great many natives' houses adjacent to troop concentrations were sprayed with DDT. Since large numbers of susceptibles, replacements from nonendemic areas, were introduced in the islands at that time, it may be presumed that the intensive mosquito control

<sup>16</sup> Essential Technical Medical Data, Headquarters, U.S. Army Forces, Far East, for March and April 1945, dated 2 June 1945. Inclosure 13 thereto.

TABLE 11.—Incidence of dengue in U.S. Army personnel in the Philippine Islands, November 1944 to December 1945

[Rate expressed as number of cases per 1,000 average strength]

Year and month	Number of cases	Rate	Year and month	Number of cases	Rate
1944			1945—Continued		
November-----	652	39.8	July-----	930	16.4
December-----	1,360	49.1	August-----	1,140	15.2
1945			September-----	439	7.9
January-----	1,023	31.8	October-----	294	6.3
February-----	893	24.8	November-----	285	6.3
March-----	1,214	25.7	December-----	89	4.1
April-----	857	19.9	Total for 1945--	8,926	15.7
May-----	913	19.6	Total-----	10,938	17.9
June-----	839	13.4			

measures were to a large extent responsible for preventing dengue epidemics in the Philippines during 1945.

**Saipan.**—The most extensive epidemic of dengue during World War II occurred in the Marianas Islands in the late summer of 1944. Fairly complete records are available only for Saipan. Dengue made its appearance soon after the assault on this island on 15 June. At first, the incidence was relatively low, probably because the rainy season had not yet begun and mosquitoes were not numerous. The rainy season began on the 1st of August, and, by the 11th of August, mosquitoes, including the vector species *A. aegypti* and *A. albopictus*, were abundant. The dengue rate (in this instance, pertains to Army, Navy, and Marine Corps personnel) among garrison troops had reached 300 per 1,000 per annum, and, thereafter, it rapidly mounted to 3,560 per 1,000 per annum on 8 September.<sup>17</sup>

Combat operations had left a multitude of breeding places for *Aedes* mosquitoes (rubble, tin cans, shell cases, and the like) in addition to the usual breeding sites (wells, cisterns, troughs, and other water containers). Although a medical sanitary company had been used for sanitation and mosquito control, cleanup was difficult during the assault phase of the campaign. After the start of the rainy season, it became evident that adequate control was impossible under existing conditions with the personnel available.

When the first supplies of DDT arrived on Saipan on 3 September 1944, it was decided to attempt area control of mosquitoes by airplane spraying of DDT solution. Improvised spraying equipment was installed in a C-47 cargo plane, and the first test run was made on 12 September. This was the first

<sup>17</sup> (1) Essential Technical Medical Data, Headquarters, U.S. Army Forces, Pacific Ocean Area, for September 1944, dated 26 October 1944. Inclosure 4 thereto. (2) Essential Technical Medical Data, Headquarters, U.S. Army Forces, Pacific Ocean Area, for March 1945, dated 19 Apr. 1945. Inclosure 5 thereto.

time airplane spraying with DDT was used over an entire island. Between 13 and 22 September, in 31 flights, 8,600 gallons of 5 percent DDT in kerosene were sprayed over a total of 15,650 acres in 3 areas, an average rate of approximately 0.2 pounds of DDT per acre. At the same time, application of DDT residual spray was begun in all tents and living quarters of hospitals and air force and garrison troops.<sup>18</sup>

Accurate statistics regarding the occurrence of dengue on Saipan are not available for the early phase of the epidemic. The daily number of new cases occurring after 13 September are recorded in table 12. The number began to decrease significantly about 1 week after airplane spraying of DDT was started. After 1 October, the number of new cases was less than one-tenth the number which occurred at the height of the epidemic. It was estimated that about 20,000 cases (which included Army, Navy, and Marine Corps personnel) of dengue had occurred on Saipan up to 20 October.<sup>19</sup>

TABLE 12.—Daily report of new cases<sup>1</sup> of dengue at height of the epidemic in Saipan, 14 September to 6 October 1944

Date	Number	Date	Number
1944		1944—Continued	
September 14-----	393	September 26-----	62
15-----	426	27-----	87
16-----	294	28-----	79
17-----	306	29-----	71
18-----	289	30-----	44
19-----	275	October 1-----	36
20-----	230	2-----	33
21-----	137	3-----	27
22-----	137	4-----	28
23-----	112	5-----	32
24-----	93	6-----	23
25-----	81		

<sup>1</sup> Cases include Army, Navy, and Marine Corps personnel.

Surveys made before and after airplane spraying of DDT indicated a great decrease (up to 98 percent) in the number of adult mosquitoes as measured by the biting rate per minute. Also it was generally agreed by troops that a tremendous reduction in the mosquito population had been effected. Since the number of new cases decreased markedly before the end of the rainy season and at a time when susceptible troops were still arriving on the island, it was concluded that the mosquito control measures employed, especially those directed against the adult insects, were responsible for the subsidence of the epidemic.

<sup>18</sup> Essential Technical Medical Data, Headquarters, U.S. Army Forces, Pacific Ocean Area, for September 1944, dated 26 Oct. 1944. Inclosure 5 thereto.  
<sup>19</sup> See footnote 17(2), p. 38.



**China-Burma-India.**—Although the area endemic for dengue included most of the theater, the majority of cases among U.S. troops occurred in the region of Calcutta. There was a definite seasonal incidence in that locale, the greatest number of cases occurring during the months from July to October, the peak varying with the dates of the monsoon.<sup>20</sup> In the theater as a whole the incidence of dengue was greatest in 1943 and 1944, with average rates of 25 and 31 respectively, per 1,000 per annum; in 1945, the incidence was approximately one-fourth that of the previous year. Although it is difficult to state definitely the causes for the reduced rate in 1945, it is believed that a large part of the improvement may be attributed to the malaria control detachments which included *Aedes* mosquitoes in their mosquito control activities. Also, all types of antimosquito supplies and equipment were more available in 1945, and individual protective measures were better enforced.

A sharp outbreak of dengue occurred after V-J Day at Hankow, China, which illustrates the degree to which the disease could incapacitate key military forces at an inconvenient time. An epidemic of dengue during September 1945 was reported to have affected 80 percent of the population of the city, including Japanese naval personnel. When American Forces occupied the airport, 40 of the first 48 men to arrive contracted dengue within 5 to 10 days.<sup>21</sup> A survey revealed numerous mosquitoes, predominantly *A. aegypti*, in this locality. In view of the dengue situation, it was first recommended that no operations be conducted from Hankow. However, use of the airport was deemed essential. The city of Hankow was declared "out of bounds," a malaria control unit was ordered into the area to undertake mosquito control measures, and personal protective measures were rigorously enforced. Apparently these steps were successful, for no further cases were reported among Americans.

## Part II. Research Activities

*Albert B. Sabin, M.D.*

Most of the basic and significant contributions to our knowledge of dengue before World War II were made by members of the Medical Department of the U.S. Army. Ashburn and Craig<sup>22</sup> provided the evidence for the viral etiology of the disease. Siler, Hall, and Hitchens<sup>23</sup> clearly established the

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<sup>20</sup> History of Preventive Medicine, Headquarters, U.S. Army Forces, India-Burma Theater, 1942-45. [Official record.]

<sup>21</sup> Essential Technical Medical Data, Headquarters, U.S. Forces, China Theater, for October 1945, dated 14 Nov. 1945.

<sup>22</sup> Ashburn, P. M., and Craig, C. F.: Experimental Investigations Regarding the Etiology of Dengue Fever. *J. Infect. Dis.* 4: 440-475, June 1907.

<sup>23</sup> Siler, J. F., Hall, M. W., and Hitchens, A. P.: Dengue: Its History, Epidemiology, Mechanism of Transmission, Etiology, Clinical Manifestations, Immunity, and Prevention. *Philippine J. Sci.* 29: 1-304, January-February 1926.



period of infectivity of dengue patients for *A. aegypti* mosquitoes, the period required for the development of the virus in these mosquitoes before they could transmit the infection, as well as the very long period during which these mosquitoes were capable of transmitting dengue. Simmons, St. John, and Reynolds<sup>24</sup> established (1) the role of *A. albopictus* in the transmission of dengue, (2) the occurrence of inapparent infection in certain monkeys under experimental and possibly also natural conditions, thus suggesting the existence of a jungle type of dengue fever exclusive of the human cycle, (3) the persistence of immunity to the homologous strain of virus for 13 months in human volunteers residing in an endemic region, and (4) many of the properties of the virus. It is necessary to recall, however, that these latter investigators completed their studies in 1930, before most of the important, newer virological techniques and procedures had been developed. In 1934, Snijders, Postmus, and Schüffner<sup>25</sup> reported some immunity experiments on human beings in Holland with two different strains of virus which left the subject of immunity to dengue in a rather uncertain state. In 1936, Shortt, Rao, and Swaminath<sup>26</sup> reported the successful cultivation of dengue virus on the chorio-allantoic membrane of chick embryos, but their conclusions were not based on tests on human beings. Otherwise, little or no work was done on dengue between 1930 and 1940.

Thus, while a good deal of fundamental information about dengue was available at the beginning of World War II, it was also apparent that most of the elementary requirements for carrying out systematic studies with the virus of dengue fever were lacking. No strains of the virus were anywhere available; there was neither a suitable laboratory animal for experimental work nor an established method of in vitro cultivation; and almost nothing was known regarding some of the basic physical and biologic properties of the virus.

From the point of view of military preventive medicine, there was a great need for an immunizing agent capable of protecting against dengue, preferably in a manner analogous to that achieved by the yellow fever vaccine. Another great need was for some practical, specific diagnostic test which would permit one to determine the precise role of dengue in the causation of the large number of "fevers of undetermined origin" encountered in dengue endemic regions. It was clear that these needs could not be fulfilled until a great deal more was learned about the basic properties of the virus, the immunity which follows natural infection, and the immunologic characteristics of strains from different parts of the world.

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<sup>24</sup> Simmons, J. S., St. John, J. H., and Reynolds, F. H. K.: Experimental Studies of Dengue. *Philippine J. Sci.* 44: 1-253, January 1931 (Monograph 29 of the Bureau of Science, Manila).

<sup>25</sup> Snijders, E. P., Postmus, S., and Schüffner, W.: On the Protective Power of Yellow Fever Sera and Dengue Sera Against Yellow Fever Virus. *Am. J. Trop. Med.* 14: 519-545, November 1934.

<sup>26</sup> Shortt, H. E., Rao, R. S., and Swaminath, C. S.: Cultivation of the Viruses of Sandfly Fever and Dengue Fever on the Chorio-Allantoic Membrane of the Chick Embryo. *Indian J. M. Res.* 23: 865-870, April 1936.

## ORGANIZATION OF DENGUE RESEARCH UNIT <sup>27</sup>

Two basic principles for the organization of a dengue research unit were apparent from the beginning: (1) that no satisfactory work could be done without a constant, fairly large supply of human volunteers located within a relatively short distance from the laboratory, and (2) that it was better to carry on the work in a dengue-free area of the United States, bringing the viruses to the research unit, than to bring the research unit to an area where dengue was occurring in our troops. The unit was organized by this writer early in 1944, at a time when he was already engaged in studies on sandfly fever in human volunteers. The work was begun in the laboratory at the Children's Hospital Research Foundation, University of Cincinnati College of Medicine, utilizing patients in need of fever therapy at the Longview State Hospital in Cincinnati, Ohio. Since the number of such patients was small, and most of those requiring fever therapy had already been used for tests with sandfly fever, the unit was transferred to New Jersey.

The human volunteers in New Jersey were white Americans who were serving sentences for civilian offenses at the New Jersey State Prison at Trenton. The authorities of the State prison very kindly donated a hospital unit of 17 beds, which was mosquito-proofed and used for housing the volunteers during the specified periods of experimentation. Two nurses (one day and one night) and a clinical laboratory technician assisted in the work of the hospital unit. The laboratory facilities were located at the Rockefeller Institute for Medical Research, near Princeton, N.J., approximately 15 miles from the hospital unit in Trenton. Lt. (later Capt.) William G. Jahnes, SnC, was assigned to the unit as the entomologic associate, and Lt. (later Capt.) R. Walter Schlesinger, MC, joined the unit as a virologic associate. Several civilian technical aides were made available by the Rockefeller Institute.

## RECOVERY OF STRAINS OF DENGUE VIRUS FROM HAWAII, NEW GUINEA, AND INDIA AND CRITERIA FOR IDENTIFICATION

During 1944 and 1945, seven strains of dengue virus were recovered from Americans stationed in Hawaii (one strain), New Guinea (four strains), and India (two strains) by subinoculation of serum specimens into human volunteers in the United States. The strains were recovered from serum specimens

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<sup>27</sup> The great interest of Brig. Gen. James S. Simmons, MC, Chief of the Preventive Medicine Service in the Surgeon General's Office, in the establishment of such a unit; the indefatigable help of Brig. Gen. Stanhope Bayne-Jones, Deputy Chief of the Preventive Medicine Service, and administrator of the Army Epidemiological Board; and the unflinching support of Dr. John R. Paul, Director of the Commission on Neurotropic Virus Diseases, were largely responsible for the creation and operation of the dengue research unit. The cooperation of the Longview State Hospital at Cincinnati, Ohio (Dr. Douglas Goldman), of the Rockefeller Institute at Princeton, N.J. (Dr. Carl Ten Broeck), and of the inmates and officials of the New Jersey State Prison at Trenton, N.J., was vital in the operations of this unit. The Army Specialized Training Program students of the University of Cincinnati College of Medicine, who volunteered for experimental inoculations in 1945, also rendered valuable service.

which were transported from overseas frozen in Dry Ice as well as from specimens which were merely refrigerated by ordinary ice. No sera were ever used in transmission tests until the patients from whom they were derived had recovered and it was clear that the clinical course was compatible with dengue. The first strain of virus was recovered in March 1944, when a pool of sera obtained from 24 to 48 hours after onset from six patients with a diagnosis of dengue during an epidemic in Hawaii was subinoculated intracutaneously in six patients at Longview State Hospital in Cincinnati.<sup>28</sup> All the subinoculated patients developed a febrile illness with rash and leukopenia, from which they promptly recovered. A large amount of serum obtained within 24 hours after onset of fever and stored partly in Dry Ice and partly in the lyophilized state served as a source of virus for many subsequent studies. Although the incubation period and clinical manifestations of the experimental disease were in most respects compatible with dengue, there was some concern about the occurrence of a rather marked, petechial eruption over the feet, ankles, legs, and in some instances over the hands and wrists, in three of the six patients toward the end of the febrile period or after defervescence. Since petechial hemorrhages had not previously been stressed in the clinical picture of dengue, it appeared necessary to determine whether or not a rickettsial agent might have been responsible. However, the convalescent sera of the six patients yielded negative results in Weil-Felix agglutination (OX-2 and OX-19) and rickettsial complement fixation tests. Inoculation of chick embryos into the yolk sac and of guinea pigs and mice with acute phase serum also failed to yield any evidence of rickettsiae. However, the identification of the virus as dengue was not considered established until transmission by *A. aegypti* mosquitoes, after the characteristic extrinsic incubation period, was accomplished.<sup>29</sup> The continued occurrence of petechial hemorrhages in human volunteers after passage of the virus through mosquitoes and also after filtration through gradocol membranes with pores too small to permit the passage of rickettsiae finally eliminated the suspicion that the petechial hemorrhages might have been due to a rickettsial agent.

Sera from several types of febrile illness were collected in New Guinea between April 1944 and 13 May 1944 and forwarded by Lt. Col. (later Col.) Cornelius B. Philip, SnC, in the fluid state refrigerated by ordinary ice. The sera, which were suitable for study, were derived from essentially three types of cases:

1. Fevers of 2 to 3 days' duration followed by rapid recovery without rash which were diagnosed as febricula or F.U.O. (fever of undetermined origin).<sup>30</sup>

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<sup>28</sup> Letter, Maj. Albert B. Sabin, MC, to Brig. Gen. Stanhope Bayne-Jones, Preventive Medicine Division, Office of The Surgeon General, 26 Apr. 1944.

<sup>29</sup> Letter, Maj. Albert B. Sabin, MC, to Brig. Gen. Stanhope Bayne-Jones, Preventive Medicine Service, Office of The Surgeon General, 9 June 1944, subject: Further Report of Certain Properties of the Hawaiian Dengue Virus.

<sup>30</sup> Credit for stimulating interest in this group of patients is due to the many medical officers in the field who in reporting these cases indicated their suspicion that the viruses of sandfly fever or dengue, or some other virus, might be responsible.



2. Fevers of 4 to 6 days' duration without rash which were regarded as dengue.

3. Fevers of 24 to 36 hours' duration, without rash, with leukocytosis of 10,000 to 19,000 diagnosed as fever of undetermined origin.

It was reported that the majority of cases in New Guinea were characterized by a short febrile course, and that very few exhibited rash or "classical saddleback" fever. The results of the subinoculation tests in human volunteers in the United States were as follows:<sup>31</sup>

1. Four strains of virus were recovered which produced a febrile illness with rash, clinically compatible with dengue.

2. Two of the strains were obtained from the serum of patients who exhibited fever of approximately 2 days' duration, and the other two strains from the serum of patients who had fever of 4 days' duration or longer.

3. Although none of the five original patients in New Guinea, from whom these four strains of virus were recovered, was reported to have had a rash, all eight volunteers inoculated either with the original serum or with the first passage serum exhibited a rash and febrile course, clinically compatible with dengue.

4. The experimental disease produced in human volunteers by the New Guinea strains was generally less severe than that produced by the Hawaii strain.

5. Cross-resistance tests in human volunteers performed from 4 to 8 weeks after the initial experimental attack served to identify the New Guinea viruses with the *A. aegypti* transmitted Hawaii dengue virus, although tests carried out after longer intervals subsequent to the original infection ultimately revealed that three of the four New Guinea strains were immunologically different from the Hawaii strain.

6. No virus was recovered from a pool of serum obtained from 32 to 36 hours after onset from two patients who exhibited fever not exceeding 36 hours in duration associated with leukocytosis but without rash. The two volunteers used in this test showed no signs of illness and subsequently were proved to be susceptible to inoculation with two of the New Guinea strains of dengue. Accordingly, it was concluded that the brief, febrile illness with leukocytosis which was seen in New Guinea was most likely not a manifestation of dengue.

A variety of febrile illnesses, some with and others without rash, pleocytosis, or other changes in the cerebrospinal fluid, were occurring among U.S. personnel in India. It was not clear whether one or several etiologic agents were involved, and whether or not the viruses of sandfly fever, dengue, or one of the neurotropic viruses were among these agents. Col. Herrman L. Blumgart,

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<sup>31</sup> Letter, Maj. Albert B. Sabin, MC, to Preventive Medicine Service, Office of The Surgeon General, attn: Brig. Gen. Stanhope Bayne-Jones, dated 3 Aug. 1944, subject: Isolation of Several Strains of Dengue Virus from Serum of Patients with Various Types of Fevers in New Guinea.



MC, medical consultant in the India-Burma theater, obtained serum and cerebrospinal fluid from a number of such patients, and the specimens, frozen in Dry Ice, were transported by air to the dengue laboratory in the United States. The clinical histories of some of the cases, particularly those occurring during the latter part of September 1945 in Calcutta, were compatible with dengue, and it was considered worthwhile to attempt isolation of new strains of virus for immunologic comparison with viruses already available from other parts of the world.

Serum from individual patients, rather than pools, was used for transmission studies to permit detection of multiple etiologic agents and correlation of the clinical picture presented by the original patient with any virus that might be isolated. When pleocytosis was present, human transmission studies were postponed until it could be shown that neither the serum nor the cerebrospinal fluid contained an agent pathogenic for mice. The human transmission tests, summarized in table 13, yielded two strains of virus.<sup>32</sup> Both strains were recovered from the filtered serum (500 m $\mu$  gradocol membrane) of two individual patients, who became ill in Calcutta on 25 September and 27 September 1945, respectively. The cerebrospinal fluid yielded no virus, although in one instance it was obtained 2 days after onset at a time when the blood of the same patient (K) contained virus. No virus was recovered from the serum of the patient in New Delhi who exhibited a pleocytosis, and it may be pointed out that his clinical history was also not compatible with a diagnosis of dengue because he had a moderate leukocytosis instead of a leukopenia. Both strains of virus from India were identified as dengue on the basis of the following properties:

1. The clinical manifestations of the experimentally transmitted disease included skin lesions, which appeared after a suitable incubation period at the sites of intracutaneous injection of the serum, a self-limited fever after an incubation period that is usual for dengue, transitory leukopenia with the usual changes in the leukocytic formula, generalized macular or maculopapular rash, and terminal petechial eruption.

2. Transmission of a clinically similar illness by *A. aegypti* mosquitoes after an extrinsic incubation period of 14 days, following feeding on human beings infected with this virus.

3. Resistance of human beings recovered from infection with known dengue virus to inoculation with these new strains.

4. Human beings infected with the Calcutta strains developed neutralizing antibodies for the Hawaii mouse-adapted virus.

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<sup>32</sup> Letter, Lt. Col. Albert B. Sabin, MC, to Preventive Medicine Service, Office of The Surgeon General, attn: Brig. Gen. Stanhope Bayne-Jones, dated 28 Dec. 1945, subject: Isolation and Identification of Two Strains of Dengue Virus From "Fevers" Among U.S. Army Personnel in India.

TABLE 13.—*Data of two strains of dengue virus obtained from patients in India with fever, isolated and identified through human transmission tests*

Patient (donor)	Hospital data				Specimen tested	Days after onset specimen obtained	Volunteer recipient	Isolation of virus						Identification of virus		
								Fever				Leuko- penia	Rash	Pass- age	Immuno- logic	A. aegypti trans- mission
	Duration of fever (days)	Rash	Cerebrospinal fluid	Diagnosis				+ or 0	Incu- bation period (days)	Maxi- mum °F.	Dura- tion (days)					
K-----	5 to 6-----	+	Protein, 64 mg. percent.	F.U.O.-----	2	B-----	+	5	103.4	5	+2,000	0	}	+	+	
W-----	4 to 5-----	0	Normal	Dengue	2	S-----	+	4	101.4	2	+3,350	0		+	+	+
P-----	4 to 5-----	+	Cells, 0; protein 50 mg. percent.	do-----	4	Br-----	+	12	102.8	5.5	+4,150	+	+	+	+	
D-----	4 to 5-----	+	Normal	do-----	4	A-----	0									
						M-----	0									
						G-----	0									
						C-----	0									
B-----	6 to 7-----	+	do-----	Denguelike fever.	5	H-----	0									
						Co-----	0									
H-----	5-----	0	135 cells, 70 per- cent lymph, Pandy +.	None-----	3											

NOTE.—Patients K, W, P, D, and B were hospitalized at the 1424 General Hospital, Calcutta, India; H was hospitalized at the 100th Station Hospital, New Delhi, India. Volunteer recipients A, M, G, C, H, and Co subsequently proved susceptible to virus.

SOURCE: Modification of table from Letter, Lt. Col. Albert B. Sabin, MC, to Preventive Medicine Service, Office of The Surgeon General, attn: Brig. Gen. Stanhope Bayne-Jones, dated 28 Dec. 1945, subject: Isolation and Identification of Two Strains of Dengue Virus From "Fever" Among U. S. Army Personnel in India.

## PROPERTIES OF DENGUE VIRUSES DETERMINED BY STUDIES ON HUMAN VOLUNTEERS

**M.I.D. (minimum infective dose) and pathogenic effects of minimal amounts of virus.**—Serum obtained from experimentally infected persons within the first few hours after onset of fever was stored in a Dry Ice chest and constituted the source of virus. The determination of the amount of virus present in such serum was desirable not only to permit quantitative work with this virus but also to ascertain whether minimal doses of virus produced a modified clinical syndrome and whether “subclinical” doses were immunogenic. Such infected serum, even after varying periods of storage in Dry Ice and repeated freezing and thawing, was found to contain 1 million human M.I.D. per milliliter, when the dilutions were made in 10 percent normal human serum-saline and inoculated intracutaneously. Ten M.I.D. injected intracutaneously produced as severe an infection as did 1 million M.I.D. However, one M.I.D. of virus produced different results in different individuals: (1) A typical unmodified attack resulted in two of four volunteers, (2) a short febrile illness without rash, followed by solid immunity, occurred in one of four volunteers, and (3) no evidence of infection, that is, neither symptoms, fever, nor leukocytic changes followed by a partial immunity to reinfection in the fourth volunteer.

**Cutaneous lesions and the local sparing phenomenon.**—Intracutaneous injection of 0.1 to 0.2 ml. of human serum, containing 10 or more M.I.D. of dengue virus, was regularly followed after an interval of 3 to 5 days by local edema and erythema, from 1 to 4 cm. in diameter. This skin lesion invariably appeared one or more days before onset of fever, and, as a rule, disappeared before the occurrence of the generalized maculopapular or scarlatiniform eruption. However, when the generalized rash did appear, a striking sparing phenomenon was observed at the sites of the original skin lesions which stood out as blanched zones surrounded by the diffuse rash. This sparing was specific in that normal human serum or other irritants did not give rise to the same phenomenon. The specificity of the dengue skin lesion and its dependence on local viral multiplication were further demonstrated by the fact that no lesion occurred when a suitable number of M.I.D. of dengue virus were mixed with homologous convalescent serum prior to inoculation, or when the virus was inoculated into dengue convalescents. Injection of convalescent serum into an established maculopapular or scarlatiniform rash failed to cause blanching.

The local irritation and small papules resulting from the bites of dengue-infected *A. aegypti* mosquitoes could not be distinguished from those resulting from the bites of uninfected *A. aegypti* mosquitoes. However, when the generalized rash occurred, it was more marked at the sites originally bitten by the normal mosquitoes, while each papule resulting from the bite of an infected mosquito was surrounded by a blanched halo. Biopsies performed on the local skin lesions showed that the epithelium was not involved and no inclusion bodies were found. The chief abnormality was found in and about the small



blood vessels and consisted of endothelial swelling, perivascular edema, and infiltration with mononuclear cells.

**Particle size of the virus.**—The diameter of the virus as determined by filtration of highly infectious human serum through gradocol membranes was estimated at 12 to 25  $m\mu$ , because all the volunteers who received the filtrates from membranes with an A.P.D. (average pore diameter) of 75  $m\mu$  or greater developed typically severe dengue, while two volunteers who received the filtrate from the membrane with an A.P.D. of 50  $m\mu$  remained well.<sup>33</sup> However, since the latter volunteers exhibited a partial immunity to reinoculation several months later, it is possible that approximately one M.I.D. of virus might have passed the 50  $m\mu$  membrane, and that the virus may actually be somewhat smaller than 17 to 25  $m\mu$ . The virus could be sedimented from human serum by centrifugation at 24,000 r.p.m. for 90 minutes in an 8-inch rotor of a vacuum ultracentrifuge. Examination with the electron microscope of preparations from highly infectious human dengue serum, purified by differential centrifugation, revealed dumbbell-shaped structures (700  $m\mu$  x 20–40  $m\mu$ ), which were not found in similar preparations from normal human serum (studies carried out in association with Captain Schlesinger, and Dr. Wendell M. Stanley of the Rockefeller Institute).

**Cultivation in various media in vitro.**—Although successful cultivation of dengue virus on the chorio-allantoic membrane of the developing chick had been claimed, the claims were either not substantiated by tests on human beings,<sup>34</sup> or the human tests which were carried out yielded [in this writer's opinion] no conclusive evidence that the cultured material was dengue virus.<sup>35</sup> Numerous attempts were made to propagate a variety of strains of the human, unmodified virus in embryonated eggs inoculated by various routes, or in tissue cultures containing minced chick embryo, minced mouse embryo, or human leukocytes. However, all of these attempts yielded negative results as judged by tests on human volunteers who failed to develop either disease or immunity. After the dengue virus was successfully adapted to propagation in mice, it proved possible to cultivate it in chick embryos.

**Experimental illness following infection with dengue virus by scarification of skin, conjunctival, or nasal instillation.**<sup>36</sup>—The investigation of the results of infection by "unnatural" routes was part of a search for some means of producing immunity without disease. Undiluted, infectious serum rubbed into the scarified skin produced unmodified dengue. Nasal instillation of 1 million or 100,000 M.I.D. (based on infectivity by intracutaneous route)

<sup>33</sup> See footnote 29, p. 43.

<sup>34</sup> See footnote 26, p. 41.

<sup>35</sup> Kimura, R., Higashi, N., and Akazawa, H.: Über die Zuchtung des Denguevirus auf der Chorioallantoismembran von Hühneriern. *Japanese J. Med. Sc. VI. Bact. and Parasitol.* 2: 241, 1944.

<sup>36</sup> Letter, Lt. Col. Albert B. Sabin, MC, to Preventive Medicine Service, Office of The Surgeon General, attn: Brig. Gen. Stanhope Bayne-Jones, dated 26 Jan. 1945, subject: Penetration of Dengue Virus Through Normal Nasal Mucosa With Resulting Modification in Clinical Type of Infection.

resulted in a very mild or negligible illness with rash in four of six human volunteers, while two others suffered from a typical, unmodified attack. Nasal instillation of 10,000 M.I.D. produced neither disease nor immunity. Instillation of 200,000 M.I.D. into the conjunctival sac produced typical dengue in one volunteer, while 10,000 M.I.D. produced neither disease nor immunity in another. Mosquitoes feeding on a volunteer with the modified, negligible disease following nasal instillation of the virus, at the time the rash first appeared (in absence of fever), developed the capacity to transmit the unmodified disease. About 5 weeks after nasal instillation of the virus, three of the volunteers, who exhibited the mildest symptomatic reaction, were exposed to the bites of dengue-infected mosquitoes and were found to be immune.

**Effect of Atabrine and penicillin.**—The effect of Atabrine (quinacrine hydrochloride) on the course of dengue was investigated in order to determine whether or not this drug might have been responsible for the mild forms of dengue encountered in our troops in New Guinea.<sup>37</sup> Three volunteers were given 0.1 gm. of Atabrine daily for a period of 12 days prior to infection by exposure to the bites of 22 to 24 *A. aegypti* mosquitoes. The same dose of Atabrine was then continued throughout the incubation and febrile periods. All three volunteers, who were daily observed to swallow the drug, developed the disease without modification of the incubation period, clinical severity, rash, or duration of fever. Penicillin administered at the onset of fever (25,000 units every 3 hours, day and night) had no effect on the course of the experimental disease.

**Capacity of certain American mosquitoes to transmit dengue.**—This investigation was carried out to determine to what extent mosquitoes prevalent in the United States, other than *A. aegypti*, might be potential vectors. The feeding of any species on human volunteers, although occurring at the onset of fever, was always checked by allowing *A. aegypti* to feed simultaneously. The extrinsic incubation periods varied from 2 weeks to over 1 month. The following species of mosquitoes were found not to transmit the infection under conditions which permitted *A. aegypti* to act as an effective vector: *Aedes vexans*, *Aedes sollicitans*, *Aedes taeniorhynchus*, *Aedes cantator*, *Anopheles punctipennis*, *Anopheles quadrimaculatus*, and *Culex pipiens*.

**Preservation of virus by freezing and lyophilization.**—Dengue virus, in the form of human serum, has been found to be remarkably stable on storage in the frozen state in a Dry Ice chest, or in the lyophilized state in an ordinary refrigerator. Preparations have remained infective for a period of 5 years, the longest interval tested thus far.<sup>38</sup>

<sup>37</sup> Letter, Lt. Col. Albert B. Sabin, MC, to Preventive Medicine Service, Office of The Surgeon General, attn: Brig. Gen. S. Bayne-Jones, dated 25 Jan. 1945, subject: (a) Effect of Daily Intake of Atabrine on Clinical Course of Experimental Dengue in Human Volunteers; (b) Factors Responsible for Mild, Usually Rash-Free, Short Febrile Forms of Dengue in New Guinea (1944).

<sup>38</sup> Sabin, A. B.: The Dengue Group of Viruses and Its Family Relationships. *Bact. Rev.* 14: 225-232, September 1950.

## EFFECT OF DENGUE VIRUS ON LABORATORY ANIMALS

Infant mice and hamsters, newborn and adult guinea pigs, cotton rats, rabbits, and *Macaca rhesus* monkeys inoculated intracerebrally or intra-abdominally, or both, with serum or whole blood of proved infectivity for human beings exhibited no clinical signs of infection. Tests with guinea pig brain tissue in a human volunteer revealed no evidence of inapparent infection in the guinea pig. On the other hand, subinoculation of serum obtained from *M. rhesus* monkeys 6 days after inoculation of human serum produced typical dengue in a human volunteer, thus confirming the occurrence of inapparent infection in *M. rhesus* monkeys. The ultimate adaptation of the virus in mice will be described subsequently.

## IMMUNOLOGIC STUDIES ON HUMAN VOLUNTEERS

**Immunity to reinfection with homologous and heterologous strains of virus.**—Human volunteers reinoculated with the same strain of virus proved to be completely immune for as long as 18 months after a single infection—the longest period tested thus far. These tests are especially significant because they were carried out on human beings residing in nondengue areas, and there can be no question of the immunity having been reinforced by intercurrent, inapparent reinfection. The results of reinoculation with a heterologous strain were found to depend on the interval after the original attack. Active immunity to heterologous strains was, as a rule, demonstrable during the first 2 months after an attack. That this cross-immunity is most likely due to a group specific antigenic stimulus and not to nonspecific resistance resulting from a preceding febrile illness was confirmed by the fact that phlebotomus fever convalescents exhibited no such immunity to dengue. Reinfection with a different immunologic type of dengue virus approximately 2 to 3 months after a primary attack had been found to give rise to malaise and slight fever for less than 24 hours, and mosquitoes which fed on such patients acquired the capacity to transmit the unmodified disease. Group immunity was still evident for as long as 9 months after the primary attack, since volunteers who were then shown to be resistant to the homologous type reacted with a rash-free, febrile illness of 2 to 3 days' duration upon inoculation with a heterologous type of dengue virus. These modified attacks, clinically not recognizable as dengue, were proved to be dengue by both mosquito and blood transmission tests. By this method of comparison, it was found that four of the seven human strains studied, that is, the Hawaii, New Guinea "A," and two strains from India, belonged to one immunologic type or group, while the other three, all from New Guinea, belonged to another. Since more than one immunologic type of dengue virus was thus found to be present in New Guinea at the same time, it is possible that reinfection with a heterologous type of virus may have been one of the causes for the many atypical febrile illnesses which were diagnosed as fever of undetermined origin, but which were shown to be dengue by recovery of the virus.



**Demonstration of type-specific neutralizing antibodies.**<sup>39</sup>—Previous attempts by other investigators to demonstrate a neutralizing antibody in convalescent dengue serum were unsuccessful. It became apparent that the previous lack of success was at least in part due to the fact that unknown quantities of virus were used in the tests. Thus, it proved possible to demonstrate that the serum of volunteers convalescent from infection with the Hawaiian strain of dengue virus was capable of neutralizing 1,000 but not 100,000 M.I.D. of virus. This means that when 0.9 ml. of convalescent serum was mixed with 0.1 ml. of acute dengue serum (with 1 million M.I.D. per milliliter) diluted 1:100, and the mixture, after *in vitro* incubation, was injected intracutaneously in 0.2 ml. amounts in a human volunteer, neither local lesions nor illness developed. Utilizing the skin surface of the arms, abdomen, and back, 20 to 40 different sera, including normal controls, could be tested simultaneously in a single volunteer, the presence or absence of neutralizing antibody in a given specimen being determined by the appearance or non-appearance of a local lesion. Neutralizing antibody against 1,000 M.I.D. of virus was demonstrated in the serum of Hawaii dengue convalescents obtained 1 week, and 1, 2, 3, and 8 months after defervescence. The dermal neutralization tests which established the type-specificity of the antibody were performed with approximately 10 minimal skin-lesion-producing doses. The results obtained in tests with five human strains of virus, shown in table 14, indicate only two distinct immunologic types among them—the Hawaii and New Guinea “A” belonging to one type, and the New Guinea “B,” and “C,” and “D” strains to another. Convalescent serum obtained during the first 2 months after an attack, when active immunity to heterologous types was readily demonstrable, contained only type-specific antibody in the dermal neutralization test.

TABLE 14.—*Differentiation between strains of dengue virus (dermal neutralization tests in human volunteers)*

Strain of virus	Skin lesions resulting from mixture with—					
	Normal serum	Human convalescent serum				
		Hawaii	New Guinea “A”	New Guinea “B”	New Guinea “C”	New Guinea “D”
Hawaii-----	+	0	0	+	+	+
New Guinea “A”-----	+	0	0	+	+	+
New Guinea “B”-----	+	+	+	0	0	0
New Guinea “C”-----	+	+	+	0	0	0
New Guinea “D”-----	+	+	+	0	0	0

Source: Sabin, A. B.: The Dengue Group of Viruses and Its Family Relationships. *Bact. Rev.* 14: 225-232, September 1950.

<sup>39</sup> Letter, Lt. Col. Albert B. Sabin, MC, to Preventive Medicine Service, Office of The Surgeon General, attn: Brig. Gen. Stanhope Bayne-Jones, dated 26 Jan. 1945, subject: Neutralizing Antibodies in Dengue and the Capacity of Different Strains of the Virus to Stimulate Their Production.

**Interference between 17-D strain of yellow fever and dengue viruses.**<sup>40</sup>—The investigation on the relationship between the yellow fever and dengue viruses was undertaken to determine whether or not vaccination with the 17-D strain of yellow fever virus can modify the clinical course and severity of dengue. This was carried out in search for an explanation for the mild form which dengue assumed in American troops in New Guinea. Thirty volunteers were used in this study and the following results were obtained:

1. When dengue virus, in amounts of 10 to 1 million human M.I.D., was inoculated simultaneously with, or 3 days after, yellow fever vaccine, the onset of dengue was delayed for 3 to 6 days, and the resulting disease was milder and of shorter duration.

2. When the dengue virus was injected 1 week after the yellow fever vaccine, the incubation period was unaffected, but the resulting disease was milder and of shorter duration.

3. When infection with dengue virus (either by the bites of infected mosquitoes or the inoculation of 10 human M.I.D. of infectious serum) was postponed for 5 weeks after the yellow fever vaccine, neither the incubation period nor the duration or severity of the resulting dengue was modified.

It was concluded, therefore, that immunity to yellow fever, resulting from vaccination of human beings with the 17-D strain of yellow fever virus, neither protects against nor modifies the disease resulting from infection with dengue virus. While a definite interference phenomenon was demonstrable during the period of propagation of the two viruses, and while the simultaneous injection of yellow fever vaccine and dengue virus resulted in a rather mild and modified form of dengue, it could not be regarded as a feasible method for the simultaneous immunization against both diseases.

## INTERFERENCE BETWEEN DENGUE AND VISCEROTROPIC YELLOW FEVER VIRUS IN RHESUS MONKEYS AND MOSQUITOES

One of the reasons the problem of interference between these two viruses was pursued further is the peculiarity in the epidemiology of yellow fever that it has apparently spared many parts of the world (for example, India, Indonesia, Australia, and so forth) where dengue has been endemic. The study on *M. rhesus* monkeys and on mosquitoes was carried out in association with Dr. Max Theiler of the International Health Division of the Rockefeller Foundation.<sup>41</sup> In the tests on human volunteers, the yellow fever virus (17-D) was

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<sup>40</sup> Letter, Maj. Albert B. Sabin, MC, to Preventive Medicine Service, Office of The Surgeon General, attn: Brig. Gen. Stanhope Bayne-Jones, dated 6 Nov. 1944, subject: Interference and Immunologic Relationship Between Dengue and Yellow Fever Viruses—Summary of Results Obtained in Studies on Human Beings, Rhesus Monkeys, and *Aedes aegypti* mosquitoes.

<sup>41</sup> See footnote 40.

the agent which produced the inapparent infection while dengue produced the clinically apparent disease. In the tests on *M. rhesus* monkeys, the dengue virus (highly infectious human serum injected intra-abdominally or intracerebrally) produced the inapparent infection while the viscerotropic yellow fever virus (Asibi strain) produced the clinically severe, fatal disease. When the dengue virus was injected in *M. rhesus* monkeys 2 or 3 days before the viscerotropic yellow fever virus, it interfered with the multiplication of the latter virus and six of seven monkeys survived, while all nine control monkeys, inoculated with yellow fever virus only, died. When the interval between the dengue and yellow fever inoculations was from 4 to 7 days, there was still demonstrable interference with the multiplication of the yellow fever virus, but death of the monkeys, while postponed, was not prevented. When the yellow fever virus (100 minimum lethal dose) was injected 1 month after the dengue virus, six of eight monkeys died in a manner which suggested that no significant cross-immunity existed between the two viruses.

Since the *A. aegypti* mosquitoes serve as natural vectors for both the dengue and the yellow fever viruses, and since available evidence indicated that mosquitoes remain infected for life, the possible occurrence of interference between these two viruses in mosquitoes was of special interest and possible epidemiologic significance. *A. aegypti* mosquitoes which first were proved to have become infected with dengue virus (by tests on human volunteers) were allowed to feed on monkeys infected with the highly virulent, Asibi strain of yellow fever virus. After a suitable interval, these mosquitoes were tested for their capacity to transmit yellow fever, and two of the three monkeys bitten by them died of yellow fever. However, tests in which extracts of individual mosquitoes were tested in mice suggested that some of the dengue-infected mosquitoes did not become infected with the yellow fever virus, while all the normal mosquitoes did. In view of the fact that in feeding on monkeys infected with the Asibi strain of yellow fever virus, each mosquito acquires about 10 million M.L.D. (minimum lethal dose) of virus, a degree of infection which may not obtain in nature, other experiments were performed in which normal and dengue-infected mosquitoes were allowed to feed on artificial mixtures containing varying amounts of yellow fever virus, and the multiplication of virus in them determined by tests in mice. These experiments strongly suggested interference with multiplication of smaller doses (about  $10^5$ LD<sub>50</sub> or less) of yellow fever in dengue-infected mosquitoes, and in another biting test in monkeys, the normal mosquitoes which ingested  $10^5$ LD<sub>50</sub> of virus transmitted yellow fever, while a similar number of dengue-infected mosquitoes which fed on the same mixture did not. These results suggested the possibility that the introduction of yellow fever virus in a dengue-endemic area may find enough mosquitoes relatively refractory to the yellow fever virus to prevent the establishment of yellow fever in the same area.



## ADAPTATION AND PROPAGATION OF DENGUE VIRUS IN MICE

The following quotation from this writer's report to the Fourth International Congresses on Tropical Medicine and Malaria <sup>42</sup> summarizes the experiences encountered in the adaptation of dengue virus to mice:

\* \* \* the many similarities between the viruses of yellow fever and dengue and the available knowledge of the varying behavior of yellow fever virus in mice, were, in large measure, responsible for the persistence with which my associate, Dr. R. W. Schlesinger, and I continued the work on adaptation of dengue virus in mice in the face of many failures. Ultimately, it appeared that in the primary adaptation of human dengue virus in mice, the important factors were the breed and age of the mice, the strain of virus, and the proportional concentration of virus and inhibitory factor apparently present in infectious human serum. The best results were obtained with the Hawaii virus, either concentrated by ultracentrifugation at 25,000 revolutions per minute for 90 minutes, or with highly infectious human serum diluted 1:100. The so-called Webster Swiss mice were better than other albino mice, and the "dba" mice bred at the Jackson Memorial Laboratory at Bar Harbor, Maine, appeared to be better than any of the albino and colored (C-57 black, C-57 brown) mice that were tested. Two-week-old or younger mice were needed for the initial passages, and it was not until the virus was thoroughly adapted after many serial passages in young mice, that older mice would succumb with regularity. The diagram in chart 2 shows that only that portion of the passage-tree which yielded successful consecutive passages and not the hundreds of mice which in the early passages exhibited nothing or yielded nothing on further passage. Only 10 to 20 percent of the inoculated mice at first exhibited clinical signs of the infection (slight weakness of the extremities detectable only by special tests in some, and distinct flaccid paralysis or encephalitic signs in others), and the incubation period was frequently 3 to 4 weeks. It took 15 passages before 100 percent of the mice inoculated with a 10 percent brain and cord suspension succumbed, and the incubation period was reduced to 9 to 14 days. At this stage the 50-percent morbidity and mortality endpoint in mice did not exceed  $10^{-2}$ , but continued serial passages in young mice gradually increased the titer and shortened the incubation period until now, after more than 80 such passages, the intercerebral titer for the 0.03 cubic centimeters dose in mice is  $10^{-5.5}$ , and the incubation period for the highest concentration is approximately 6 days. We could not be certain that this virus in mice was indeed dengue virus, until, after appropriate preliminary tests in laboratory animals, the early passage material was inoculated in human volunteers and produced in them solid immunity to unmodified human dengue virus. Similarly, we know that the virus of higher potency which is now being passaged in mice is still dengue virus, because it is neutralized specifically by the human convalescent sera and by the sera of rhesus monkeys and chimpanzees inoculated with human virus that has never been through mice. This mouse-adapted dengue virus produces neither apparent nor inapparent infection in cotton rats, hamsters, guinea pigs, or rabbits.

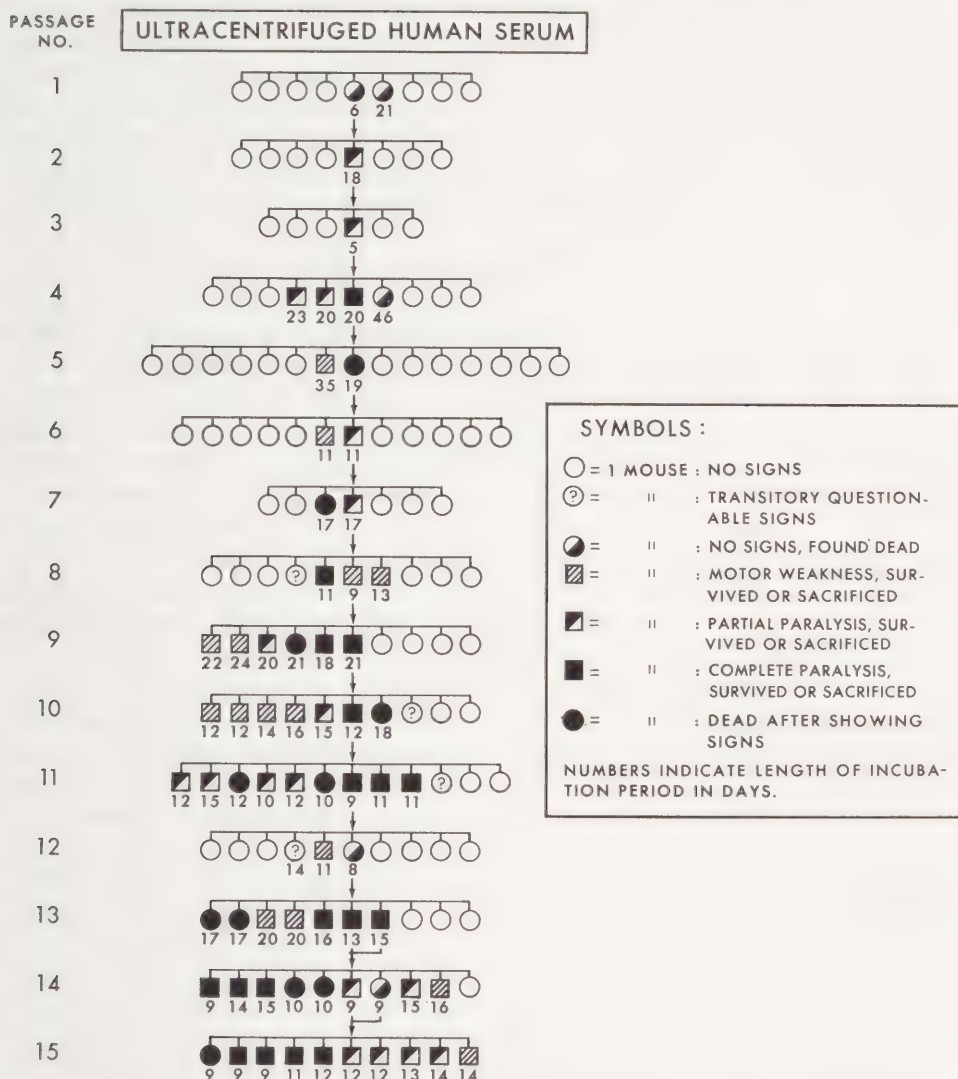
### EFFECT ON HUMAN VOLUNTEERS OF MOUSE-PROPAGATED DENGUE VIRUS AT DIFFERENT STAGES OF ADAPTATION

Extracts of the brain and spinal cord of paralyzed mice, derived from the first six consecutive passages in mice, upon inoculation in human volunteers produced clinical manifestations of varying severity—relatively mild in some

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<sup>42</sup> Sabin, A. B.: Recent Advances in Phlebotomus and Dengue Fevers. *Proc. Fourth Internat. Cong. Trop. Med. and Malaria* 1: 520-525, May 1948.

CHART 2.—Adaptation of dengue virus (Hawaii strain) to Swiss albino mice



and fully severe and unmodified in others.<sup>43</sup> Local skin lesions appeared at the sites of intracutaneous injection after an incubation period of 5 to 7 days, and marked generalized maculopapular and ultimately petechial eruptions appeared in all. Leukopenia with the qualitative and quantitative changes in the leukocytic formula usually seen in dengue were also present. Blood serum obtained from the above volunteers at the onset of the generalized eruption produced typical dengue in another volunteer.

<sup>43</sup> Sabin, A. B., and Schlesinger, R. W.: Production of Immunity to Dengue With Virus Modified by Propagation in Mice. *Science* 101: 640-642, June 1945.

Beginning with the seventh passage in mice, however, the virus had lost its capacity to produce the severe illness and protracted fever, characteristic of the unmodified disease in human beings, but retained its capacity to produce a rash and solid immunity to the unmodified virus. Fever either did not occur, or was low-grade, lasting 24 hours, or less. Blood taken from such persons at the time the rash first appeared produced only the same type of modified reaction in other volunteers. Immunity to infection with the unmodified virus was already present 12 days after inoculation, the shortest interval tested.

## USE OF MOUSE-ADAPTED DENGUE VIRUS AS A VACCINE

The results of tests on nine human volunteers inoculated with the 7th to the 10th mouse-passage virus indicated that the virus had undergone sufficient attenuation to permit its consideration for use as a vaccine against dengue. Accordingly, two vaccines were prepared from the 15th and 19th mouse-passage virus and tested both in ASTP (Army Specialized Training Program) medical student volunteers and in schizophrenic patients. The 15th mouse-passage vaccine,<sup>44</sup> consisting of a centrifuged 1:10 mouse-brain extract in 10-percent human serum-saline solution, was tested in 16 individuals in doses of 0.5 ml. of the 1:100, 1:1,000, and 1:10,000 dilutions. While the titer of this virus in mice was only 1:100 for the 0.03 ml. dose, all inoculated persons (including those receiving 0.5 ml. of the 1:10,000 dilution) developed a maculopapular eruption of varying extent, while systemic symptoms were either absent, negligible, or very mild; 21 to 38 days after vaccination, all were found to be immune upon exposure to *A. aegypti* mosquitoes of proved infectivity. Thus, it became apparent that the extract from a single mouse brain and cord, preserved in the frozen state, had enough antigen in it to immunize at least 10,000 people. When some of the same 15th mouse-passage vaccine was lyophilized together with yellow fever vaccine and tested in 10 students (the inoculum contained 1:100 or 1:1,000 dengue and the standard dose of yellow fever vaccine), 5 of 7 students subsequently exposed to dengue-infected mosquitoes were not immune. It was not clear whether the chick embryo yellow fever vaccine did not constitute a suitable protective agent for the lyophilization of the diluted, modified dengue virus, or whether the proportions of the two viruses in the inoculum were such that the multiplication of the smaller dose of modified dengue virus was suppressed by the larger dose of yellow fever virus.

Since it was desirable to get away from human serum as a constituent of the vaccine, crystalline bovine albumin was selected as the protein to be used for both extraction and lyophilization in the tests with the 19th mouse-passage vaccine.<sup>45</sup> A relatively large amount of vaccine (enough for more than 50,000

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<sup>44</sup> Report, Lt. Col. Albert B. Sabin, MC, and Capt. R. W. Schlesinger, MC, to Meeting of the Commission on Neurotropic Virus Diseases, Army Epidemiological Board, 18 Oct. 1945, subject: Vaccination of Human Beings with Dengue Virus Modified by Passage in Mice.

<sup>45</sup> Letter, Capt. R. W. Schlesinger, MC, to Brig. Gen. Stanhope Bayne-Jones, Preventive Medicine Service, Office of The Surgeon General, 12 Sept. 1945, with Appendix I, "Results of Immunity Tests."



men) was prepared both as a model for production on a still larger scale and for the purpose of having enough available for a field trial if the preliminary human tests were satisfactory. With the aid of the facilities of the laboratories of the International Health Division of the Rockefeller Foundation, the vaccine was lyophilized in two forms—as 10 percent and as 1 percent extract of mouse brain and cord in 10 percent crystalline bovine albumin. Simultaneous titrations in mice of the frozen and lyophilized 10 percent vaccines revealed that the lyophilized material had only one-tenth as much infective virus as the frozen preparation; that is, that 90 percent of the infectivity was lost on lyophilization. However, tests on 15 persons revealed that the 10 percent lyophilized vaccine produced the same type of reactions (that is, predominantly rash) as the 15th mouse-passage frozen vaccine, except that in the 1:10,000 dilution the lyophilized preparation produced rash in only 1 of 3 individuals, and immunity to a large dose of unmodified dengue virus (probably as much as 1 million M.I.D.) in 2 of the 3 individuals. The 1 percent lyophilized vaccine was apparently ineffective (probably more deterioration on lyophilization) since neither rash nor immunity resulted from the 1:1,000 or the 1:10,000 doses.

Each vial of the 10 percent lyophilized vaccine contained 1 ml. of the centrifuged extract of mouse brain and cord, and was to be reconstituted in 20 ml. of saline. Thus, 0.1 ml. of this diluted material (the projected dose for subcutaneous injection) contained the mouse brain and cord extract as well as the crystalline bovalbumin in a final dilution of 1:200, and one vial would have supplied enough vaccine for approximately 200 men. This vaccine was to be used in a field trial among troops who were being transferred from Europe to the Pacific, but the war fortunately came to an end before this eventuality occurred.

## INFECTIVITY OF *A. AEGYPTI* MOSQUITOES FEEDING ON HUMAN BEINGS INOCULATED WITH MOUSE-ADAPTED DENGUE VIRUS

This investigation was prompted by two practical questions: (1) Is it possible that the virus might revert to its original, unmodified virulence after passage through mosquitoes, and (2) could *A. aegypti* mosquitoes transmit the modified infection after feeding on vaccinated individuals at certain periods after inoculation? The following results were obtained:

1. *A. aegypti* mosquitoes which fed on the human volunteer inoculated with the 2d and 3d mouse-passage virus (that is, before fixed modification had occurred) during the period of low-grade fever produced unmodified dengue in another volunteer after an extrinsic incubation period of 22 days, but not after 15 days, even though 40 mosquitoes fully engorged.

2. *A. aegypti* mosquitoes which fed on people inoculated with the 10th mouse-passage virus acquired the capacity to transmit the modified infection; that is, the bitten volunteer developed only the rash and leukopenia without fever or other significant symptoms.

3. Extensive tests carried out on students, inoculated with the 15th mouse-passage virus, indicated that several lots of *A. aegypti* mosquitoes, which had fed daily on the experimental subjects for 14 days after vaccination, were unable to transmit the infection even after prolonged extrinsic incubation periods of 29 to 33 days. With 22 to 42 mosquitoes engorging in the tests on each volunteer, there was no rash or other clinical evidence of infection in any of the 14 men who were exposed in these tests.

## CULTIVATION OF MOUSE-ADAPTED DENGUE VIRUS IN CHICK EMBRYOS

No success was achieved in the cultivation of dengue virus in chick embryos until the virus had undergone approximately 16 consecutive passages in mice.<sup>46</sup> Attempts to propagate the mouse-adapted virus, using passages 4, 5, and 13, in fluid or plasma clot cultures containing mouse embryo brain tissue were unsuccessful in that no virus pathogenic for mice was demonstrable after 1, 2, or 3 passages. When the 13th passage mouse-adapted virus was used for inoculation of 6- or 10-day-old chick embryos which were subsequently incubated for 8 or 4 days, respectively, at 37° C., no mouse-pathogenic virus was demonstrable after one to four serial passages. The results were the same when the inocula were introduced into the yolk sac or embryo, allantoic or amniotic sacs. When the 13th passage mouse-adapted virus was inoculated directly into the brain of 10-day-old embryos which were subsequently incubated for 7 days at 37° C., mouse-pathogenic virus was demonstrable in the chick embryo brain tissue in the first passage, but not in the second. Repetition of this procedure with 16th passage mouse-adapted virus yielded negative results even in the first passage. When the 16th or 18th passage mouse-adapted virus was used for inoculation (toward the embryo) of 5-day-old chick embryos which were subsequently incubated for 8 days at 37° C., mouse-pathogenic virus was demonstrable in whole embryo extract of the first passage in three separate series. In only one of these series, however, was virus demonstrable in the second passage, but even in this series it was no longer present in the third passage when the incubation was at 37° C. It was found, however, that incubation at 35° C. was more suitable for the serial propagation of the virus, so that it has been possible to demonstrate appreciable amounts of virus in the third passage of at least two series. There was some indication that 4 or 5 days of incubation was not as good as 8 days, and that while the virus was present in the amniotic membrane as well as in the whole embryo, little or no virus was found in the amniotic fluid.

It finally proved possible to obtain continuous cultivation of the virus in embryonated eggs when 5-day-old embryos were used for inoculation and a

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<sup>46</sup> Report, Capt. R. W. Schlesinger, MC, and Lt. Col. Albert B. Sabin, MC, to Meeting of the Neurotropic Virus Commission, Army Epidemiological Board, 18 Oct. 1945, subject: Dengue Virus in Chick Embryos.



period of 8 to 10 days at 35° C. for incubation. Tests in four human beings with extracts of the third passage whole chick embryo or amniotic membrane revealed that the virus had remained in its modified form, producing the characteristic macular or maculopapular eruption after an incubation period of 9 to 11 days, without fever (except for elevation of 1° F. for 24 hours in one subject) or other clinical manifestations.

## SEROLOGIC TESTS WITH MOUSE-ADAPTED DENGUE VIRUS

After the Hawaii dengue virus became sufficiently adapted to mice to yield an intracerebral titer of  $10^{-3}$  to  $10^{-4}$ , it was possible to develop a mouse test for the detection of neutralizing antibody. At that stage, no neutralization of the virus could be demonstrated without preliminary incubation of the mixtures at 37° C. for 2 hours, or if the serum was heated at 56° C., for 30 minutes. Neutralization tests performed under optimal conditions (that is, with sera transported and stored in Dry Ice, and serum-virus mixtures incubated at 37° C. for 2 hours) on sera from human volunteers infected with various strains of virus and from individuals with histories of naturally acquired infections in various parts of the world yielded considerable interesting information. Thus, it was established that the neutralizing antibody was type-specific and appeared as early as 1 week after onset of illness and persisted for at least 2 years (more recently, at least 4 years) in individuals residing in nondengue areas. Neutralization tests on sera from people with a diagnosis of dengue during the Hawaii epidemic of 1943-44, or the Japanese epidemics of 1944-45, revealed that the Hawaii type of virus was probably predominant in those outbreaks, while similar tests on the sera of Americans who had the disease on Guam in 1944-45, and from Americans and Panamanians in the Panama Canal Zone indicated that another type or types of dengue were probably more prevalent there.

## TESTS FOR DENGUE DURING WORLD WAR II

**Philippines and Okinawa.**—Large numbers of cases of a febrile illness (or febrile illnesses) clinically similar to dengue, with the important exception that there was no rash, occurred in 1945 in the Philippine Islands and on Okinawa. In view of the success that was encountered in the recovery of several strains of dengue virus from clinically atypical cases in New Guinea, repeated attempts were made to demonstrate the presence of dengue virus in patients with this atypical illness in the Philippines and Okinawa. The serologic tests for dengue were not yet adequately developed at the time, and reliance had to be placed on the inoculation of serum, obtained within 24 to 48 hours after onset of fever, into human beings in the United States. Three pools of sera derived from 11 patients in Leyte, P.I. (February-March 1945), were subinoculated into 6 human beings in the United States, and two sera from 2 patients on Mindoro, P.I. (April 1945), were subinoculated into 2 human beings in the United



States,<sup>47</sup> but all the recipients remained well. Although the donor patients were selected because they remained free of jaundice, there was, nevertheless, a great deal of hepatitis in those regions at the time. It is noteworthy, therefore, that the recipients were observed for many months but did not develop jaundice. The sera of five patients from Okinawa (June–August 1945) were similarly inoculated into four human beings in the United States with completely negative results.<sup>48</sup>

**Panama Canal Zone.**—An investigation into the occurrence of dengue in Panama during World War II was carried out in January and February 1946.<sup>49</sup> It was found that in 1941 and early 1942, at a time when a great deal of new activity was in progress in the Canal Zone and when there was an influx not only of military personnel but also of laborers from adjacent countries, there was a considerable outbreak in Americans of a disease with clinical manifestations entirely compatible with a diagnosis of dengue. However, the diagnosis of dengue was not made, and practically all of these cases were found in the files of the Gorgas Hospital under the diagnoses of “nasopharyngitis,” “nasopharyngitis with rash,” or occasionally “X–Y–Z” fever. However, in 1945, Capt. (later Maj.) L. McCarty Fairchild, MC, of the Gorgas Hospital reported a selected series of these cases as “denguelike fever” in Panama.<sup>50</sup> An analysis of the charts of these patients indicated that clinically they represented classical forms of dengue. It is of interest that *A. aegypti* breeding in Ancon, Balboa, and Panama City were sufficiently high (indexes of 10 to 17 percent) to justify warnings regarding intensified mosquito control. It is furthermore of interest that during this same period the “great majority” (variously estimated as 80 percent) of the native Panamanian population in Panama City was attacked by a disease which was diagnosed for the most part as measles, German measles, or glandular fever. However, some of the Panamanian physicians<sup>51</sup> suspected dengue at the time, and this author’s examination of many of the clinical records revealed syndromes clinically characteristic of dengue. There were apparently no further outbreaks after 1942, but sporadic cases probably continued to occur since four clinically characteristic cases were observed in Americans during this author’s visit early in 1946. Neutralization tests in mice yielded positive results with three of eight convalescent sera from the 1941–42 outbreak, and one of six sera from recent convalescents. It would appear that a type of dengue virus, immunologically distinct from the Hawaiian strain, may be prevalent in

<sup>47</sup> Letter, Lt. Col. Albert B. Sabin, MC, to Preventive Medicine Service, Office of The Surgeon General, attn: Brig. Gen. Stanhope Bayne-Jones, dated 28 Dec. 1945, subject: Human Transmission Tests With Sera From F.U.O. Cases on Mindoro, P.I., During March and April 1945.

<sup>48</sup> Letter, Lt. Col. Albert B. Sabin, MC, to Preventive Medicine Service, Office of The Surgeon General, attn: Brig. Gen. Stanhope Bayne-Jones, dated 28 Dec. 1945, subject: Dengue-Like Fever on Okinawa—Human Transmission Tests.

<sup>49</sup> Letter, Albert B. Sabin, M.D., Army Epidemiological Board, to The Surgeon General, U.S. Army, through Chief, Preventive Medicine Service, 5 Mar. 1946, subject: Investigation of Fevers of Undetermined Origin in the Canal Zone and Republic of Panama With Special Reference to Possible Endemicity of Dengue and Phlebotomus (Sandfly) Fever.

<sup>50</sup> Fairchild, L. M.: Dengue-Like Fever on Isthmus of Panama. *Am. J. Trop. Med.* 25: 397–401, September 1945.

<sup>51</sup> Rognoni, M.: Epidemic Disease in Panama (Editorial). *Boletín Asociacion Medica Nacional Panama* 3: 7, 1941.

Panama. This investigation also suggested the possibility (1) that the interior of Panama may be an endemic focus of dengue, and (2) that the *Haemagogus* mosquitoes and monkeys in the jungles of Panama should be investigated as a possible source of "jungle dengue fever."

**Japan.**—According to an inquiry carried out by the writer in Japan in 1946, it would appear that approximately 2 million cases of dengue may have occurred in the port cities of Nagasaki, Kure, Sasebo, Kōbe, and Osaka between 1942 and 1945.<sup>52</sup> Dengue was said to have been unknown in Japan before 1942, and the epidemics were correlated with two facts: (1) These cities were the ports of entry for people from Shanghai, Singapore, and the Malay States where dengue was prevalent at the time, and (2) the water shortage and the later bombing led to the storage of water in all sorts of containers which became the breeding grounds for *A. albopictus*. The city of Osaka with a population of about 2 million had about 5,000 cases in 1942; 3,000 to 4,000 cases in 1943; 400,000 to 600,000 cases in 1944; and an unknown number in 1945, when, because of the air raids, the population dispersed to the surrounding villages. The situation was said to be similar in other port cities. Examination of the clinical charts of cases which occurred among the hospital personnel in Osaka revealed the classical clinical picture of dengue, and blood obtained from many of these patients in 1946 neutralized the mouse-adapted dengue virus.

Japanese investigators carried out experimental studies on dengue during the war, and many strains of virus were reported to have been adapted to a variety of experimental animals. Some of these animal-adapted viruses were no longer available in 1946. However, of five strains of "dengue" virus which were submitted by several investigators for comparative study, only the three mouse-adapted strains recovered by Drs. S. Hotta and R. Kimura of Kyōto turned out to possess the properties of dengue virus; the other two "dengue" viruses submitted by others turned out to be Rift Valley fever in one instance and fixed rabies virus in another. The neutralization tests performed with the Japanese convalescent sera indicated that the Hawaii type of virus was either predominant in, or exclusively responsible for, the epidemics in Japan.

## SUMMARY

Research on dengue in the United States during World War II provided the following new information of special interest to military preventive medicine:

1. Proof of the existence of multiple immunologic types of dengue.
2. The long persistence of immunity to homologous types of virus under conditions precluding reinforcement of immunity by subclinical reinfection.
3. The modifications of the clinical manifestations of the disease which result from reinfection with a heterologous type of virus at various periods after the primary attack.

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<sup>52</sup> See footnote 42, p. 54.

4. The demonstration that, in areas (for example, New Guinea) where more than one immunologic type of virus is present, fevers of undetermined origin, clinically not recognizable as dengue, are actually caused by the dengue viruses.

5. The demonstration that type-specific immunity to dengue is associated with neutralizing antibodies for the virus, which can be used for diagnostic and epidemiologic survey purposes.

6. The propagation of dengue virus in mice with the resulting appearance of a mutant or variant strain which could be used for active immunization.

In addition to the discoveries listed, a great deal more was learned about the basic properties of the dengue viruses. Thus was dengue research brought from the field into the laboratory, and further progress has been made possible by work on experimental animals instead of on human volunteers.



## CHAPTER V

# Filariasis Bancrofti

*John Clyde Swartzwelder, Ph. D.*

The first epidemic of filariasis in the history of American or other military forces occurred in World War II. The disease, which is caused by the filarial worm, *Wuchereria bancrofti*, appeared in American servicemen in epidemic proportions only in certain Central Pacific islands.<sup>1</sup> Many of the infections apparently were acquired on Tongareva or Penrhyn Island, Bora-Bora (Society Islands), Aitutaki (Cook Islands), Wallis Islands, Tutuila (American Samoa), Upolu (British Samoa), Tongatabu (Tonga Islands), Apamama (Gilbert Islands), and Fiji Islands (map 1).

Units of the Army and the Navy were stationed on islands in the Central Pacific Area. The Army task forces were based on Bora-Bora, Aitutaki, Tongareva, Fiji, and Tonga Islands. The Navy and Marine forces were located on Wallis, Tutuila, Upolu, and Funafuti (Ellice) Islands. As a result, both services had experience with filariasis.<sup>2</sup>

There were about 2,500 U.S. Army admissions for filariasis from 1942 through 1945. One death from filariasis was recorded in an oversea theater in 1944. The data on admissions for filariasis in the U.S. Army, by year, are significant: Three admissions in 1942, 660 in 1943, 1,585 in 1944, and 235 in 1945 (table 15). Over 12,000 cases of filariasis occurred in U.S. Navy and U.S. Marine Corps personnel.<sup>3</sup> The difference between the number of cases of filariasis in the two services was largely due to the difference in the number of personnel stationed on the islands where filariasis was a problem.<sup>4</sup>

Filariasis was of definite military significance during World War II. From 5 to 70 percent of certain groups in the Samoan Defense Area contracted the disease over a long period. It was estimated that the overall incidence of infection in American military personnel would reach 30 percent or higher among exposed troops.<sup>5</sup> Filariasis was among the leading causes of medical

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<sup>1</sup>(1) Sapero, J. J.: Epidemiological Observations on Filariasis. National Research Council, Division of Medical Sciences, Commission on Medical Research, Office of Scientific Research and Development, Tropical Diseases Report No. 17, June 1944. (2) Sapero, J. J., and Butler, F. A.: Highlights on Epidemic Diseases Occurring in Military Forces in the Early Phases of the War in the South Pacific. J.A.M.A. 127: 502-506, March 1945.

<sup>2</sup> Reports on Filariasis Bancrofti in American Forces in the Pacific Area, April 1944-January 1945, by Maj. James I. Knott, MC.

<sup>3</sup> Brown, O. J.: Late Manifestations of Tropical Diseases. Med. Ann. District of Columbia 16: 125-131 (March) 1947.

<sup>4</sup> Stevens, Frank W.: [History, World War II] Medicine—South Pacific Area, pp. 21-23. [Official record.]

<sup>5</sup> See footnote 1(2).



MAP 1.—*Filariasis bancrofti* in the Pacific area—World War II.

evacuation in the South Pacific Area. A significant loss of manpower and of money resulted directly from the disease. The general morale of troops within an endemic area as well as of those who had been staged in such areas was influenced adversely.<sup>6</sup> Intense fear of the disease by troops, almost bordering on hysteria, constituted an important military problem. Fear of elephantiasis, of sterility, and of transmission of the disease to their families, coupled with the sight of horribly deformed natives, engendered this attitude. Experience and greater knowledge of the disease have shown that these fears were unfounded.

The history of two U.S. Army organizations illustrates the loss of manpower which resulted from the military experience with filariasis. The 134th Field Artillery Battalion and the 404th Combat Engineer Company (Separate) were dispatched overseas in April 1942. They were stationed at Tongatabu from May 1942 to May 1943. The units were sent to Townsville, Australia, and then to Woodlark Island in July 1943, where they remained until January 1944. Because of the number of men exhibiting symptoms of filariasis, the units were transferred to Sydney, Australia, and were examined by the staff

<sup>6</sup> Malaria and Epidemic Disease Control Training Manual No. 6, Headquarters, South Pacific Area and Force, November 1944, subject: Filariasis, Epidemiology, and Control.

TABLE 15.—Admissions for filariasis in the U.S. Army, by theater or area and year, 1942-45

[Preliminary data based on sample tabulations of individual medical records]  
[Rate expressed as number per annum per 1,000 average strength]

Theater or area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States-----	481	0.03	0		0		391	0.10	90	0.03
Overseas:										
Europe-----	0		0		0		0		0	
Mediterranean <sup>1</sup> -----	9	.01	0		8	.02	1	0.00		0
Middle East-----	1	.01	0		0		1	.02		0
China-Burma-India-----	2	0.00	0		1	.03	1	.01		0
Southwest Pacific-----	323	.18	0		70	.37	233	.43	20	.02
Central and South Pacific-----	1,348	1.07	0		557	1.91	741	1.69	50	.13
North America <sup>2</sup> -----	1	0.00	0		1	.01	0			0
Latin America-----	307	.80	3	0.3	18	.15	216	2.52	70	.96
Total overseas <sup>3</sup> -----	2,002	0.19	3	0.01	660	0.39	1,194	0.31	145	0.03
Total Army-----	2,483	0.10	3	0.00	660	0.10	1,585	0.20	235	0.03

<sup>1</sup> Includes North Africa.  
<sup>2</sup> Includes Alaska and Iceland.  
<sup>3</sup> Includes admissions on transports.

NOTE.—The strengths on which the rates were based are mean strengths and will vary therefore from the official strength reports of The Adjutant General.  
Absolute zero is indicated by zero in the units column; 0.00 indicates a rate of more than zero but less than 0.005.

of the 118th General Hospital. A filariasis survey of the two units revealed evidence of high infection rates: 77 percent and 73.4 percent, respectively, were given as preliminary figures, which later were reduced to 65 and 55 percent, respectively.<sup>7</sup> The Commanding General of the Sixth U.S. Army recommended that the 134th Field Artillery Battalion and the 404th Combat Engineer Company (Separate) be returned to the United States for the following reasons: The combat efficiency of the units had been seriously impaired; rehabilitation would extend over an indefinite period of time; the future combat value of the two units was highly doubtful; and the replacement of all individuals showing evidence of filariasis would result in a state of training far below that required for efficient combat.<sup>8</sup> The personnel of the organizations returned to the United States as patients in July 1944. When they reached Moore General Hospital, Swannanoa, N.C., the troops had been overseas for 27 months. They had never

<sup>7</sup> Letter, Col. R. F. Brown, MC, Headquarters, 118th General Hospital, to the Chief Surgeon, Headquarters, U.S. Army Services of Supply, Southwest Pacific Area, 16 Apr. 1944, subject: Final Report of Filariasis Survey of 536 Officers and Enlisted Men From 134th Field Artillery Battalion and 173 Officers and Enlisted Men From 404th Combat Engineer Company (S), inclosure thereto, report, dated 15 Apr. 1944.  
<sup>8</sup> Letter, Lt. Gen. W. Krueger, Headquarters, Sixth U.S. Army, to the Commanding General, U.S. Army Forces, Far East, 8 Apr. 1944, subject: Return of 134th Field Artillery Battalion and 404th Engineer Company (C) (Separate) to the United States, inclosure thereto.



been in combat and had been hospitalized for 7 months. The men were confused, apprehensive, and discouraged.<sup>9</sup>

## EPIDEMIOLOGIC CONSIDERATIONS

An elucidation of the basic factors which contributed to the occurrence of epidemic filariasis is appropriate. After the Japanese attack on Pearl Harbor, troops of the Army, Navy, and Marine Corps were rushed to the Samoan Defense Area. The defenses had to be set up in great haste, and camouflage and other defense considerations had high priority. The areas which had to be defended already contained native villages, and some of the military installations were placed in the villages and camouflaged to blend into the landscape. The military authorities would have preferred to move the native population, but objections were raised by the island governments. The defense forces were instructed not to disturb the friendly relations existing between the civilians and the military forces.

Since 1900, the U.S. Navy has maintained a station on Tutuila Island. Before 1942, no cases of filariasis had been reported as occurring in military personnel stationed there, but until then, the number of American personnel on the island of course was small. In peacetime, they lived in screened tropical quarters in a sanitated area at a distance from native dwellings. A survey of the naval station area during the subsequent epidemic revealed a low density of the filarial mosquito vector, *Aedes scutellaris*. None of the specimens captured contained filarial larvae.<sup>10</sup>

There appeared to be a lack of knowledge of tropical diseases and of a general plan for control of mosquitoes. Individual preventive measures against mosquito bites apparently were inadequate.<sup>11</sup> Malaria is not endemic in the Samoan area so that any fortuitous protection from filariasis which might have resulted from malaria and mosquito control measures was lacking.

The task of prevention was complicated by the problem of diagnosis of early filariasis. Relatively few physicians, either civilian or military, had much experience with recognition of the early manifestations of the disease. Confirmation of clinical diagnosis by laboratory means during the initial phase of the infection is difficult and in many cases is not possible. As a result, there was delay in recognition of the syndrome of filariasis when it first became manifest in troops. Many of the men diagnosed as cases of filariasis probably were not actually suffering from the disease, and the diagnosis was extremely doubtful.

One must give full consideration to the fact that the military activities in the Samoan area were initiated under conditions of urgency in which tactical

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<sup>9</sup> Letter, Col. J. M. Hayman, Jr., MC, Chief, Medical Service, Moore General Hospital, Swannanoa, N.C., to The Surgeon General, attn: Tropical Disease Treatment Branch, 22 June 1945, subject: Filariasis in the 134th Field Artillery Battalion and the 404th Combat Engineer Company.

<sup>10</sup> See footnote 2, p. 63.

<sup>11</sup> Report of Medical Department Activities on Aitutaki, Cook Islands, 27 July 1944, by Capt. T. D. Englehorn, MC.

defense measures demanded highest priority. However, the number of cases of filariasis which developed is evidence that the hazard of filariasis was not fully appreciated nor was it adequately anticipated.

Excellent epidemiologic investigations were conducted by Byrd, St. Amant, and Bromberg.<sup>12</sup> They observed that as high as 25 percent of the mosquito species, *A. scutellaris* var. *pseudoscutellaris*, which were collected in the center of native villages in the Samoan area contained infective larvae. As collections were made at successively distant points from the village, the natural mosquito infection rate dropped to zero at a distance of 200 yards. Their observations indicated that infected mosquitoes had a short flight range and did not travel far from the site where they had taken a blood meal. This suggested that the degree of transmission might largely depend upon the degree of intermingling of natives and troops.

Epidemic filariasis occurred in troops only in the South and Central Pacific islands where the following conditions obtained: (1) *Microfilariae* of the parasite were "non-periodic" (actually diurnal), (2) the vector was a day-biting *Aedes* mosquito which was present in considerable numbers, and (3) there was intimate intermingling of infected natives and troops. In contrast, filariasis occurred only sporadically in other Pacific islands, such as the New Hebrides, Solomons, and New Guinea, despite the fact that a high incidence of malaria, another mosquitoborne disease, was acquired by troops in these islands.<sup>13</sup>

## CONTROL OF EPIDEMIC FILARIASIS

The following measures were taken to control epidemic filariasis: All units were required to set up a mosquito control organization. Each unit supplied enlisted men and a noncommissioned officer who worked under the direction of a mosquito control officer. Malaria control units were diverted from malaria control to filariasis control. Insect repellent and insecticides were made available in adequate supply. Camp areas were moved as far as possible from native villages. Troops were prohibited from visiting villages, and natives were excluded from camps. When the tactical situation permitted, as many troops as possible were removed from the islands. It was recommended that troops which remained were to be rotated to temperate or nonfilarial islands after a period of 10 to 12 month's duty.<sup>14</sup> The precipitous decline in the number of reported cases of filariasis in the latter part of 1944 indicated that effective measures were being taken to prevent infection with or to avoid exposure to filariasis.

A striking example of the value of observing the principles of military sanitation was demonstrated by Lt. Gen. Thomas E. Watson, U.S. Marine

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<sup>12</sup> Byrd, E. E., St. Amant, L. S., and Bromberg, L.: Studies on Filariasis in the Samoan Area. U.S. Nav. M. Bull. 44: 1-20, January 1945.

<sup>13</sup> See footnote 1(1), p. 63.

<sup>14</sup> Letter, Maj. Gen. Norman T. Kirk, The Surgeon General, U.S. Army, to the Commanding General, South Pacific Theater, attn: The Surgeon, 5 Nov. 1943, subject: Filariasis. First indorsement thereto, dated 21 Nov. 1943.

Corps,<sup>15</sup> on the island of Upolu. About 90 percent of the forces on this island were located in a camp around a large airfield. Natives were prohibited from entering the military area. Effective mosquito control measures were carried out in the camp area. Only rare cases of filariasis developed in the men in this camp, and these infections probably were not acquired in the camp area. About 10 percent of the island garrison were stationed at defense positions in the town of Apia and at outlying radar posts. These troops were located near natives, and a number of the personnel acquired filariasis.

The troops on Funafuti escaped filariasis due, in part and indirectly, to aerial attacks by the Japanese. The island was bombed by the Japanese several times soon after the first American troops arrived. The natives were moved to another island 8 miles away for their safety. Subsequently, there was an outbreak of dengue fever. In order to control this disease, a mosquito control program was undertaken. Later, when the island was surveyed, not a single *A. scutellaris* mosquito was found.<sup>16</sup>

In March 1944, Maj. James I. Knott, MC, was assigned to investigate filariasis in the Pacific and to make recommendations in regard to prevention and diagnosis and to management of cases already contracted. He submitted a series of reports, which included a review of the filariasis problem in the Samoan area and survey data on filariasis among native reservoirs of infection on many Pacific islands.<sup>17</sup>

Prevention of filariasis was not limited to the prevention of new infections. A wise precaution was taken to minimize the possibility of the development of complications which might result from exposure to infection over a long period of time. Tropical diseases, such as filariasis, which are liable to exacerbation or serious aggravation upon reinfection were designated as disqualifying defects for duty in tropical areas<sup>18</sup> and later for any oversea area.<sup>19</sup>

The dispatch of prisoners of war from Pacific islands where filariasis is heavily endemic to Hawaii and to continental United States raised the question of the possible hazard of introduction of the disease into these nonendemic areas. Between June 1945 and the cessation of hostilities in August 1945, over 4,000 prisoners of war from Okinawa were received in the Hawaiian Islands. *Microfilaria* were found in 16 percent of the prisoners.<sup>20</sup> It was promptly recommended that any Okinawan prisoners of war who had reached or who might reach those areas be returned to one of the islands of the western Pacific

<sup>15</sup> See footnote 2, p. 63.

<sup>16</sup> See footnote 2, p. 63.

<sup>17</sup> (1) See footnote 2, p. 63. (2) Report on Filariasis Bancrofti in the Military Forces in the Pacific Area, 10 Aug. 1945, by Maj. James I. Knott, MC. (3) Report on Filariasis Bancrofti in the Marshall Islands (Report of a Visit to Kwajalein Atoll, 24 Aug. to 8 Sept. 1944), by Maj. James I. Knott, MC. (4) Report on Filariasis Bancrofti on the Solomon and New Hebrides Islands, 2 Dec. 1944, by Maj. James I. Knott, MC. (5) Report on Filariasis Bancrofti in New Caledonia and the Loyalty Islands, 12 Dec. 1944, by Maj. James I. Knott, MC. (6) Report on Filariasis in Queensland, 18 Dec. 1944, by Maj. James I. Knott, MC.

<sup>18</sup> War Department Circular No. 189, 21 Aug. 1943.

<sup>19</sup> War Department Circular No. 293, 11 Nov. 1943.

<sup>20</sup> History of Preventive Medicine, Headquarters, U.S. Army Forces, Middle Pacific, ch. 34.



or to islands which are relatively uninhabited and where introduction of the disease would be of small consequence.<sup>21</sup>

The existence of numerous potential mosquito vectors of *W. bancrofti* in the continental United States and in Hawaii has been demonstrated by many investigators.<sup>22</sup> However, there appeared to be little reason to fear the establishment of filariasis in the United States by reason of returning servicemen.<sup>23</sup> The Army has maintained a followup of men infected with filariasis to determine whether any appreciable number would show microfilariae in the blood at a later date. Microfilariae have been found in the peripheral blood in only a very few of the infected veterans. At one time, filariasis was frequently encountered in the United States, having been imported with slaves from West Africa. However, the disease was unable to perpetuate itself in this country and disappeared spontaneously about 1925. This experience coincides with a similar episode in Queensland, Australia, where the disease was introduced by infected laborers from some Pacific islands and from China. From the past history of filariasis in the United States and in Australia, one can predict that filariasis will not become endemic in this country despite the return of infected military personnel from overseas.

## DEVELOPMENTS IN FILARIASIS CONTROL DURING WORLD WAR II

A valuable though expensive lesson in preventive medicine can be gained from the military experience with filariasis bancrofti in World War II. New medical weapons for the prevention and control of filariasis have been developed. Use of the lessons derived from the epidemic of filariasis in troops and of the new developments of value for the prevention and control of the disease should militate against a repetition of the past military experience with filariasis bancrofti.

<sup>21</sup> Letter, Col. Arthur B. Welsh, MC, Headquarters, U.S. Army Forces, Middle Pacific, to The Surgeon General, U.S. Army, 31 July 1945, subject: Filariasis in Okinawan Prisoners of War. First indorsement thereto, dated 14 Aug. 1945.

<sup>22</sup>(1) Newton, W. L., Wright, W. H., and Pratt, I.: Experiments to Determine Potential Mosquito Vectors of *Wuchereria bancrofti* in the Continental United States. *Am. J. Trop. Med.* 25: 253-261, May 1945. (2) Scott, O. K., Richards, C. S., and Seaman, E. A.: Experimental Infection of Southern California Mosquitoes With *Wuchereria bancrofti*. *J. Parasitol.* 31: 195-197, June 1945. (3) Newton, W. L., and Pratt, I.: Experiments to Determine Potential Mosquito Vectors of *Wuchereria bancrofti* in the Continental United States. *Am. J. Trop. Med.* 26: 699-706, September 1946. (4) Nelson, E. C., Webb, J. E., Bayliss, M., and Starkey, G. S.: Studies of Filariasis; Development of *Wuchereria bancrofti* in *Culex quinquefasciatus* of Oahu. *Am. J. Trop. Med.* 26: 707-713, September 1946. (5) Eyles, D. E., and Most, H.: Infectivity of Pacific Island *Wuchereria bancrofti* to Mosquitoes of the United States. *Am. J. Trop. Med.* 27: 211-220, March 1947.

<sup>23</sup>(1) Coggeshall, L. T.: Filariasis in the Serviceman: Retrospect and Prospect. *J.A.M.A.* 131: 8-12, May 1946. (2) McCoy, O. R.: Filariasis in Military Personnel. *Trop. Med. News* 3 (No. 2): 4-6, April 1946. (3) McCoy, O. R.: Public Health Implications of Tropical and Imported Diseases; Imported Malaria. *Am. J. Pub. Health* 34: 15-19, January 1944. (4) McCoy, O. R.: Precautions by the Army to Prevent the Introduction of Tropical Diseases. *Am. J. Trop. Med.* 26: 351-355, May 1946. (5) Brown, H. W.: Current Problems in Filariasis. *Am. J. Pub. Health* 35: 607-613, June 1945.

Segregation of troops from natives is of extreme importance to avoid transmission of the disease to military personnel. Control of the mosquito vectors, which may differ in various areas in regard to species and to breeding, resting, and feeding habits, is requisite. Mosquito control measures should be directed not only at the destruction of adult mosquitoes but also at the elimination of breeding sites of the aquatic stages. New insecticides, including DDT, which have residual action against adult mosquitoes, have improved the means for mosquito control.<sup>24</sup> Field studies of the effect of DDT residual house spraying have been conducted in one endemic area of filariasis where *Culex quinquefasciatus* was the vector. The spraying program resulted in a reduction in the number of mosquitoes, a decreased filarial infection rate of the insect vector and a fall in both the incidence of microfilaria-positives and the number of microfilariae per case in the DDT-sprayed area.<sup>25</sup> Numerous U.S. Army medical publications concerning the use of DDT have been published for guidance of all concerned with disease vector control.<sup>26</sup> Improved mosquito repellents afford more effective protection of troops against the bites of mosquitoes.<sup>27</sup> Individual aerosol insecticide dispensers and mobile aerosol generators should facilitate the destruction of adult mosquito vectors and increase the protection of troops from filarial infection. Adequate screening, use of bed nets, and wearing of full-length clothing are of obvious value.

Recent evidence has been presented which indicates that transmission of filariasis in American Samoa may be primarily in the bush, along the trails, and in the plantations. The possible role of these types of environments in other Pacific islands, where this same infection and same mosquito vector occur, should be considered in relation to prevention and control of this disease.

The discovery that Hetrazan (diethylcarbamazine) causes a reduction or complete disappearance of microfilariae from peripheral blood may offer a valuable new approach to the control of filariasis.<sup>28</sup> Field trials of Hetrazan for the control of filariasis have shown that significant reduction in total micro-

<sup>24</sup>(1) Andrews, J. M., and Simmons, S. W.: Developments in the Use of the Newer Organic Insecticides of Public Health Importance. *Am. J. Pub. Health* 38: 613-631, May 1948. (2) Andrews, J. M.: Advancing Frontiers in Insect Vector Control. *Am. J. Pub. Health* 40: 409-416, April 1950. (3) Hinman, E. H.: Public Health Interests in Insecticides, Repellents, Rodenticides and Herbicides. *Proc. South. Branch, Am. Pub. Health A.*, pp. 9-17, April 1949.

<sup>25</sup>(1) Kohler, C. E.: Filariasis Control by DDT Residual House Spraying, Saint Croix, Virgin Islands; I. Operational Aspects. *Pub. Health Rep.* 64: 857-862, July 1949. (2) Brown, H. W., and Williams R. W.: Filariasis Control by DDT Residual House Spraying, St. Croix, Virgin Islands; II. Results. *Pub. Health Rep.* 64: 863-875, July 1949.

<sup>26</sup>(1) War Department Technical Bulletin (TB MED) 142, February 1945. (2) War Department Technical Bulletin (TB MED) 110, 25 Oct. 1944. (3) War Department Technical Bulletin (TB MED) 194, 17 Aug. 1945. (4) War Department Technical Bulletin (TB MED) 14, 3 Mar. 1944. (5) War Department Technical Bulletin (TB MED) 164, June 1945. (6) War Department Technical Bulletin (TB MED) 182, July 1945.

<sup>27</sup>Knipling, E. F., and Dove, W. E.: Recent Investigations of Insecticides and Repellents for the Armed Forces. *Bull. War Med.* 5: 776, August 1945.

<sup>28</sup>Santiago-Stevenson, D., Oliver-González, J., and Hewitt, R. I.: Treatment of Filariasis Bancrofti With 1-Diethylcarbamyl-4-Methylpiperazine Hydrochloride ("Hetrazan"). *J.A.M.A.* 135: 708-712, November 1947.

filaremia and of microfilaria-positives follows the use of the drug.<sup>29</sup> As a result of therapy, the rate of infected mosquitoes was drastically reduced. Use of Hetrazan may prove to be an extremely valuable adjunct measure for the prevention and control of filariasis bancrofti. Treatment of infected natives which would constitute a reservoir and potential source of infection for troops may now be considered as a possible means of reducing transmission of filariasis bancrofti.

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<sup>29</sup>(1) Hewitt, R., Kenney, M., Chan, A., and Mohamed, H.: Follow-up Observations on the Treatment of Bancroftian Filariasis With Hetrazan in British Guiana. *Am. J. Trop. Med.* 30: 217-237, March 1950. (2) Hewitt, R. I., White, E., Hewitt, D. B., Hardy, S. M., Wallace, W. S., and Anduze, R.: The First Year's Results of a Mass Treatment Program With Hetrazan for the Control of Bancroftian Filariasis on St. Croix, American Virgin Islands. *Am. J. Trop. Med.* 30: 443-452, May 1950. (3) Maldonado, J. F., Morales, F. J., Herrera, F. V., and Thillet, C. J.: The Role of Hetrazan in the Control of Filariasis Bancrofti. *Puerto Rico J. Pub. Health & Trop. Med.* 25: 291-299, March 1950.





## CHAPTER VI

# Leishmaniasis

Henry E. Meleney, M.D.

The two general types of leishmaniasis, cutaneous and visceral, are entirely different clinically, and somewhat different in geographic distribution. Their occurrence in the U.S. Armed Forces during World War II is, therefore, presented separately.

## CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis includes two main clinical forms: Oriental sore, caused by *Leishmania tropica* and occurring in the Old World, and the mucocutaneous form caused by *Leishmania braziliensis* and occurring in tropical America. The two forms are not tabulated separately in the tables which follow, but it can be assumed for practical purposes that only those cases admitted to installations in Latin America were the mucocutaneous form.

Table 16 presents the recorded incidence of cutaneous leishmaniasis among U.S. Army active-duty personnel by theater and year of admission, 1942-45, based on sample tabulations of individual medical records by the Medical Statistics Division, Office of The Surgeon General. It includes only inpatients

TABLE 16.—Incidence of cutaneous leishmaniasis (including mucocutaneous) among U.S. Army active-duty personnel, by theater or area and year, 1942-45

[Preliminary data based on sample tabulations of individual medical records]  
[Rate expressed as number of cases per annum per 1,000 average strength]

Theater or area	1942-45		1942		1943		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States.....	11	0.02	0		0		6	0.00	5	0.00
Overseas:										
Europe.....	21	0.00	0		1	0.00	10	0.01	10	0.00
Mediterranean <sup>1</sup> .....	15	.01	0		0		10	.02	5	.01
Middle East.....	281	2.11	0		94	1.77	172	3.72	15	.54
China-Burma-India.....	12	.03	0		1	.03	11	.07		0
Southwest Pacific.....	29	.02	0		1	.01	28	.05		0
Central and South Pacific.....	59	.04	0		4	.01	55	.13		0
North America <sup>2</sup> .....	0		0				0			0
Latin America.....	9	.02	3	.03	3	.02	3	.03		0
Total overseas.....	426	0.04	3	0.01	104	0.06	289	0.08	30	0.00
Total Army.....	437	0.02	3	0.00	104	0.02	295	0.04	35	0.00

<sup>1</sup> Includes North Africa.

<sup>2</sup> Includes Alaska and Iceland.

NOTE.—Absolute zero is indicated by zero in the units column; 0.00 indicates a rate of more than zero but less than 0.005.

and is, therefore, an underestimate, because most cases, at least in the Middle East theater, were treated as outpatients. This will be presented in detail in this chapter. Cases were recorded from all theaters of operations except North America outside the United States. Since cutaneous leishmaniasis is not known to be endemic in the Southwest Pacific or Central and South Pacific Areas, cases recorded from those areas either were acquired elsewhere or were erroneously diagnosed. The accuracy of the data from other theaters may also have been affected by troop movements, long incubation periods, and the difficulty of diagnosis under military conditions.

Table 16, presenting statistics based on hospital records (WD, MD Form 86ab), shows only 437 cases of cutaneous leishmaniasis occurring in U.S. Army personnel in all theaters and areas during the period 1942-45, and shows that the largest number of cases occurred in the Middle East theater of operations. As stated in the preceding paragraph, these figures are known to be far too low. A more accurate indication of the total number of cases and their predominant concentration in the Middle East theater are given in table 17 which is taken from the Essential Technical Medical Data, Persian Gulf Command, for December 1944, dated 19 January 1945. The explanation of the manner in which these statistics were collected is, in the words of the chief of the Medical Branch of the Persian Gulf Command, as follows:

**Leishmaniasis.**—Early in the month it was noted that the reported cases of this disease on the Statistical Health Report Form 86ab were too low in comparison to the number of cases that were being treated in the Ahvāz area. Investigation revealed that many cases were being treated on an outpatient status and were not being carded for record only so that they would be picked up on the 86ab. Instructions were immediately issued that all of these cases so treated would be carried and reported. In addition, all medical installations were to check their outpatient records and submit to this office a report by months of cases so treated but not previously reported. These reports have been received and consolidated in this office and the following table [table 17] lists the total cases of this disease since October 1943:

TABLE 17.—*Incidence of cutaneous leishmaniasis, Persian Gulf Command, by month, October 1943-December 1944*

[Rate expressed as number of cases per annum per 1,000 average strength]

Month and year	Number of cases	Rate	Month and year	Number of cases	Rate
<i>1943</i>			<i>1944—Continued</i>		
October.....	3		June.....	4	
November.....	237	105	July.....	12	5
December.....	235	83	August.....	6	1
<i>1944</i>			September.....	26	9
January.....	158	70	October.....	35	12
February.....	72	32	November.....	26	12
March.....	24	8	December.....	41	15
April.....	7	4	Total.....		888
May.....	2				



The peak rates in November and December 1943 and January 1944 occurred from 2 to 3 months after the end of the season in which there was the greatest abundance of sandflies (*Phlebotomus*).<sup>1</sup> It was believed that most of the cases had been contracted in the vicinity of Ahvāz, a town on the Kārūn River near the head of the Persian Gulf. The accuracy of diagnosis of these cases is assured by the report of Ball and Ryan<sup>2</sup> on 499 cases at the 113th General Hospital, in all of which *Leishmania* were demonstrated in stained smears from lesions. All except two of these cases were in U.S. Army personnel. All except 27 were treated as outpatients. Ball and Ryan calculated that the incubation period varied from 10 days to 6 weeks. Because some of their cases had proved lesions within 3 days after arrival and had spent about a month in India and 10 days in transit, they assumed that these cases had originated in India. The number of lesions per patient varied from 1 to 29 with an average of 4.3. Since soldiers often slept naked, lesions occurred on all parts of the body including fingers, toes, and penis.

### VISCERAL LEISHMANIASIS (KALA-AZAR)

Table 18 presents the incidence of kala-azar among U.S. Army active-duty personnel by theater and year of admission, 1942-45, based on sample tabulations of individual inpatient medical records. The data are probably fairly accurate since kala-azar is a severe clinical disease requiring hospitalization. All of the known cases acquired the infection either in the western Mediterranean area or in India, in or near Calcutta. Most and Laviates<sup>3</sup> reviewed 30 of these cases which received treatment or followup examinations at Moore General Hospital, Swannanoa, N.C. Of these, 15 had originated in India and 15 in the Mediterranean theater. Of the latter, 14 had served in North Africa and Italy, or in North Africa, Italy, and Sicily long enough before the onset of symptoms to have acquired the infection in any one of these areas. One case was apparently contracted at Nice. In other cases, the men had slept in huts or trucks in or near native villages in North Africa. Among the cases from India, two occurred in officers who had shared an apartment in Calcutta, and three others in a company quartered at an airbase on the outskirts of Calcutta.

The shortest known incubation period recorded by Most and Laviates was 12 weeks, and the longest was in a veteran who left the Mediterranean endemic area 19 months before the onset of symptoms. A considerable number of patients did not develop symptoms until after they had left the endemic area, and a few not until after they had been discharged from military service. In two cases which resisted all forms of chemotherapy, splenectomy was per-

<sup>1</sup> Monthly Sanitary Report, Persian Gulf Command, 4 Jan. 1944.

<sup>2</sup> Ball, D., and Ryan, R. C.: Cutaneous Leishmaniasis. Bull. U.S. Army M. Dept. 79: 65-73, August 1944.

<sup>3</sup> Most, H., and Laviates, P. H.: Kala-Azar in American Military Personnel: Report of 30 Cases. Medicine 26: 221-284, September 1947.

TABLE 18.—*Incidence of visceral leishmaniasis among U.S. Army active-duty personnel, by theater or area and year, 1942-45*

[Preliminary data based on sample tabulations of individual medical records]  
 [Rate expressed as number of cases per annum per 1,000 average strength]

Theater or area	1942-45 <sup>1</sup>		1944		1945	
	Number of cases	Rate	Number of cases	Rate	Number of cases	Rate
Continental United States.....	11	0. 00	5	0. 00	5	0. 00
Overseas:						
China-Burma-India.....	34	0. 08	9	0. 05	25	0. 11
Mediterranean <sup>2</sup> .....	13	. 01	8	. 01	5	. 01
Middle East.....	1	. 01	1	. 02	-----	0
Central and South Pacific.....	1	0. 00	1	0. 00	-----	0
Other.....	-----	0	-----	0	-----	0
Total overseas.....	49	0. 00	19	0. 00	30	0. 01
Total Army.....	60	0. 00	24	0. 00	35	0. 00

<sup>1</sup> Only one case of visceral leishmaniasis was reported during 1942-43; the case was admitted in continental United States in 1942.

<sup>2</sup> Includes North Africa.

NOTE.—Absolute zero is indicated by zero in the units column; 0.00 indicates a rate of more than zero but less than 0.005.

formed. One of the patients<sup>4</sup> was in good health after splenectomy without further chemotherapy. The other patient died 13 months after splenectomy, which was 5 years and 3 months after the initial diagnosis, with repeated courses of chemotherapy.<sup>5</sup> *Leishmania* were still demonstrable in the organs at autopsy. All other known cases apparently were cured after one or more courses of chemotherapy.

## TRANSMISSION

The vectors of *Leishmania* are known to be various species of the sandfly *Phlebotomus*. *Phlebotomus papatasi* has been incriminated in the transmission of oriental sore in the Middle East and *Phlebotomus argentipes* in the transmission of kala-azar in India. Epidemiological and entomological studies by Hertig and others, during World War II, showed that *P. papatasi* was constantly associated with outbreaks of sandfly fever amongst U.S. Army troops in the Middle East and in Sicily, and, at the same time, experimental studies

<sup>4</sup> Burchenal, J. H., Bowers, R. F., and Haedicke, T. A.: Visceral Leishmaniasis Complicated by Severe Anemia—Improvement Following Splenectomy. *Am. J. Trop. Med.* 27: 699-709, November 1947.

<sup>5</sup> Personal communication, Harry Most, M.D., Professor of Preventive Medicine, New York University College of Medicine, to Henry E. Meleney, M.D., Research Professor of Medicine, Louisiana State University, School of Medicine, 22 Mar. 1955.

by Sabin and associates proved that *P. papatasi* was capable of transmitting the virus, while certain mosquitoes were unable to do so. (See pp. 119, 121 and pp. 142, 148.)

Reservoir hosts probably play an important part in maintaining *Leishmania* infections in certain areas, wild rodents for oriental sore in the Middle East, and dogs for kala-azar in the Mediterranean region.

## PREVENTIVE MEASURES

No special measures of control were employed against leishmaniasis, although measures taken against sandfly fever, which was very prevalent in the Persian Gulf Command, were undoubtedly effective in the prevention of leishmaniasis. These measures consisted of the use of the sandfly net (30 meshes to the linear inch), insect repellent (Rutgers 612 (2-ethyl-1, 3-hexanediol), dimethyl phthalate, and Indalone (butopyronoxyl), or a mixture of the three), pyrethrum sprays, the Freon-pyrethrum Aerosol, and, beginning in 1944, residual spraying with DDT. It is probable that the use of these measures was responsible for the lower incidence of oriental sore in the Persian Gulf Command during the last few months of 1944.

Hertig made experimental studies of *Phlebotomus* control with residual DDT, first with Fairchild<sup>6</sup> in Peru in 1943-44 and later with Fisher<sup>7</sup> in Italy and Palestine. It was found that, because the *Phlebotomus* flies in short hops with long pauses, it was possible to protect inhabitants of buildings by spraying the insides of rooms, all openings, and the outer walls for a foot or two around the openings. Results of experiments in tents, though incomplete, indicated comparable results. Area control within a radius of 100 to 200 yards of habitations was obtained by spraying structures such as loose-laid stone walls, which serve as breeding or resting places, and places where *Phlebotomus* would alight in flying toward a blood meal.

A survey by Hertig<sup>8</sup> in Greece, Crete, and Italy in 1949 indicated that residual DDT spraying for the control of malaria had reduced *Phlebotomus* tremendously.

The ease with which *Phlebotomus* can be prevented from biting man in permanent installations by residual DDT should make this procedure the principal means of protection against this insect in future military operations. Application of DDT on 18-mesh bed nets should obviate the necessity for the special sandfly net. Insect repellents will still be useful where other measures are unavailable.

<sup>6</sup> Hertig, M., and Fairchild, G. B.: The Control of *Phlebotomus* in Peru With DDT. Am. J. Trop. Med. 28: 207-230, March 1948.

<sup>7</sup> Hertig, M., and Fisher, R. A.: Control of Sandflies With DDT. Bull. U.S. Army M. Dept. 88: 97-101, May 1945.

<sup>8</sup> Hertig, M.: *Phlebotomus* and Residual DDT in Greece and Italy. Am. J. Trop. Med. 29: 773-809, September 1949.





## CHAPTER VII

# Plague

*Karl F. Meyer, M.D., and Oliver R. McCoy, M.D.*

The history of plague calls attention to the unpleasant truth that for centuries the waging of wars has contributed to its rise and spread. The plague of Moscow in 1771 was directly related to the return of Russian troops infected by Turkish prisoners of war as early as 1769. At the beginning of the 19th century, plague still lingered in the Levant, and Egyptian troop movements imported it in 1829 into Greece.

During the wars of the past 50 years, however, plague has played a negligible role. It did not occur among U.S. Army personnel during World War II, even though plague infected civil populations in the vicinity of troops in the Azores, Africa, and the Middle and Far East. There were, however, in the British Middle East Force,<sup>1</sup> 26 cases of bubonic plague with 5 deaths (19.2 percent) involving 12 Indians, 6 East African natives, 5 British, 1 Italian, 1 "Cape coloured," and 1 European Jew.

## PREVENTIVE AND CONTROL MEASURES

Military operations took American troops to regions where the risk of plague was extensive and constant. They encountered both the endemic and the epidemic form. The extent of plague in areas occupied by military personnel will be described in general terms, and the procedures of control will be briefly outlined.

An energetic attack on plague in the civilian populations of the areas where the soldiers were compelled to live was adopted as a general policy. Army medical officers were able to apply new methods of control made possible by discoveries in allied fields during the war. Traditional plague control directed against the animal reservoir, the rat, by energetic trapping, poisoning, elimination of their breeding places, and curtailment of their food supply, was gradually displaced by flea disinfestation of premises and persons with the insecticide DDT. The Preventive Medicine Service, Office of The Surgeon General, made its greatest contribution to the control of plague by applying for the first time this new approach.

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<sup>1</sup> Mackay-Dick, J.: Brief Report on 26 Cases of Bubonic Plague With Results of Treatment. J. Roy. Army M. Corps 85: 105-108, September 1945.

### Zone of Interior

Periodic exacerbations of endemic rat plague in 1943 and 1944 in the port of Tacoma, Wash., offered a chance for the spread of infection. The permanent endemic of sylvatic plague in the area of the Ninth Service Command was recognized as another possible source of danger to troops. Rodent control measures carried out in close cooperation with the U.S. Public Health Service and the health departments of the various States minimized these potential hazards. Field studies conducted by the staff of the George Williams Hooper Foundation, San Francisco, Calif., incident to these control measures led to valuable ecologic observations. It is not generally known that pools of fleas and organs of rats (*Rattus norvegicus*) were systematically tested, particularly in the western seaports, and that latent plague was discovered in these specimens in the City of San Francisco, Oakland, and near Richmond, Calif. (1943), and Tacoma, Wash. (1942-44). Ectoparasites or tissues from rodents at Fort Cronkhite, Camp Mendell, and Fort Baker, Marin County, Calif. (1942), at Fort Ord, Calif., and the Hunter Liggett Military Reservation, south of Salinas, Calif., and near Gowen Field, Idaho, carried the plague bacillus. Extensive wild rodent surveys conducted by the California State Department of Public Health during 1942 demonstrated new pockets of sylvatic plague in counties not previously known to be infected and frequently located in the vicinity of airfields or ammunition storage places. New foci of wild rodent plague, rodent hosts, and flea vectors were uncovered by the Plague Suppressive Service of the U.S. Public Health Service in Montana, Wyoming, Colorado, North Dakota, and New Mexico. Intensive and thorough traditional control measures through poisoning as a rule reduced the rodent population to a low level and greatly diminished the risk of infection.

The incidental observation was made that in followup studies at Fort Cronkhite during October 1942 latent tularemia infection was discovered in rats (*R. norvegicus*), harvest mice (*Microtus californicus*), and field mice (*Peromyscus maniculatus*). Although the rodents were present in casemates, clinical infections in man were not evident. This apparent low communicability is of interest in view of the report on tularemia among German troops during the siege of Stalingrad.<sup>2</sup>

The Fort Ord epizootic sylvatic plague area yielded many pools of infected fleas and diseased squirrels. In 1942, burrows were thoroughly treated with carbonbisulfide, thallium-coated grain, and zinc phosphite poison. In addition to this, the area was freed of squirrels by shooting during a period of 6 months. Through splendid cooperation with the military authorities, the California State Department of Public Health and the George Williams Hooper Founda-

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<sup>2</sup> Bogendörfer, L., Saleck, W., and Kairies, H.: Über das Auftreten von Tularämieerkrankungen an der Ostfront. Deut. Militärarzt. 7: 699-673, November 1942. (2) Gaede, D., and Kairies, A.: Untersuchungen zur Epidemiologie und Diagnostik der Tularämie. Deut. Militärarzt. 8: 30-35, January 1943. (3) Schmidt, B.: Der Einbruch der Tularämie in Europa. Ztschr. f. Hyg. u. Infektionskr. 127: 139-150, 6 Jan. 1947.



tion were able to make detailed ecologic studies and record relevant useful observations.

During March 1943, plague was unexpectedly discovered in harvest mice (*M. californicus*). These rodents had apparently taken over the function of the reservoir hosts and thus maintained the infection while the squirrels hibernated. Similar ecologic adjustments incidental to the eradication measures directed primarily against the squirrel (*Citellus beecheyi*) were encountered at the Hunter Liggett Military Reservation and other areas in California.

In September and October 1942, *Pasteurella pestis* was found in fleas collected from rats trapped on the waterfront of Tacoma. Vigorous orthodox control measures were instituted by the U.S. Public Health Service against a heavy rat population, and plague was found in rats in that area for the last time in this epizootic in May 1943.<sup>3</sup> However, after nearly a year and a half of testing, during which specimens were not positive, infection was again reported in October 1944 in fleas and subsequently in tissues from rats and mice.<sup>4</sup> The last reported positive specimens were collected in December 1944.

Although the exact origin of rodent plague in Tacoma has not been determined, inductive evidence strongly incriminated grain shipments from localities of eastern Washington known to be foci of sylvatic plague. The original positive specimens were taken from an area heavily infested with rats, where railway cars filled with grain were unloaded.<sup>5</sup> The transfer of plague from forest rodents to those that inhabit man's living areas has recently been definitely proved.<sup>6</sup>

Finally, toward the end of World War II, vessels coming into New York from foreign ports were heavily infested with rats.<sup>7</sup> The usual vigilance over rat infestation in war zones, which had banished shipborne plague between 1935 and 1940, had apparently been dangerously relaxed. Although it was suspected that the French steamship *Wyoming* from Casablanca, French Morocco, carried an infected rat in January 1943, the infection did not spread to American ports through this channel. Proof was never established that the rat was infected.

Study and control measures in the United States, then, were carried out either cooperatively or independently by the Army, the U.S. Public Health Service, various State departments of health, and the George Williams Hooper Foundation. Control measures to protect military personnel against plague, beyond the customary precautions in seaports and epizootic areas, centered in

<sup>3</sup> Hundley, J. M., and Nasl, K. W.: Anti-plague Measures in Tacoma, Wash. Pub. Health Rep. 59: 1239-1255, 22 Sept. 1944.

<sup>4</sup> Hampton, B. C.: Plague Infection Reported in the United States During 1944 and Summary of Human Cases, 1900-44. Pub. Health Rep. 60: 1361-1365, 16 Nov. 1945.

<sup>5</sup> See footnote 4.

<sup>6</sup> Meyer, K. F., and Holdenried, R.: Rodents and Fleas in a Plague Epizootic in a Rural Area of California. Puerto Rico J. Pub. Health 24: 201-209, March 1949.

<sup>7</sup> (1) Olesen, R.: Increase of Rat Infestation on Vessels Coming to New York. Pub. Health Rep. 60: 1295-1296, 2 Nov. 1945. (2) Olesen, R., and Stone, J. L.: Increase of Rat Infestation on Oil Tankers. Pub. Health Rep. 60: 1296-1301, 2 Nov. 1945.

the destruction of rodents in and around military bases in the West. The threat of plague originating in the United States, certainly of no great military significance during the war, was in all probability reduced by vigilance and by decreasing the number of rodents in inhabited areas.

### Hawaii

During 1943, 1944, and 1945, human plague was, after a silent period of 3 years, again reported from the Hamakua District on the Island of Hawaii—seven fatal cases in 1943 and seven cases with five deaths in 1944. From May 1943 to April 1944, the flea index (*Xenopsylla cheopis* and *Leptopsylla segnis* Schönherr) rose from 0.17 to 0.61, and infected dead rats (mostly *R. hawaiiensis*, few *R. norvegicus*) were found with increasing frequency; for example, 12 in February and 12 in March 1944. The personnel of the Territorial Board of Health vigorously attacked the problem through a three-phase field program. A total of 4,619 persons were inoculated with the Army type of plague prophylactic. By extensive poisoning and gassing operations and community sanitation, rat-free zones were established in and around the infected area, while the rodent population was held at a low level in the epizootic area. Trapping operations were used primarily to determine whether or not the infection was spreading. The limited nature of the outbreak was treated expectantly by the Armed Forces. Air Force personnel and employees who had occasion to enter the Hamakua District had been inoculated with plague vaccine.

### Azores and East Africa

In 1942, small detachments of U.S. troops exposed to old, permanently active foci of endemic plague (16 cases in 1942 and 55 cases in 1945) in the Azores around Ponta Delgada and in the District of San Jose were included in protective measures taken by the British against the spread from the local civil populations.<sup>8</sup> Military personnel were restricted to the areas where rodent control programs were in operation and were immunized with killed plague vaccine prepared according to the method of Schütze at the Lister Institute in London. Similar control measures were taken in Kenya where the natives had suffered high losses in 1941 and 1942 (781 and 754 cases, respectively). Improvement of conditions was rapid; only 16 cases occurred among the natives during 1943 and 13 cases during 1944. The infection was confined to the Rift Valley and the Central Province. Although epizootics among field rodents had been observed, there is no sure proof that sylvatic plague was responsible for the outbreaks.<sup>9</sup>

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<sup>8</sup> Stowman, K.: Synopsis of Epidemics in Europe. V. Mediterranean Peninsula. Epidemiol. Inform. Bull. 2: 493-502, June 1946.

<sup>9</sup> Kaul, P. M.: Prevalence of Plague in the World in Recent Years. Epidemiol. & Vital Statist. Rep. 2: 143-165, August 1949.

## Dakar

During 1943, there was a small outbreak of plague among natives in the area of Dakar, French West Africa. The airport of the Air Transport Command was within the range of wandering infected rodents, a real danger. Rodent control measures were instituted at the base, restrictions were placed on movements of U.S. Army personnel in the area, and permanently assigned personnel were inoculated with U.S. Army plague prophylactic. In addition, aircrews whose duties required frequent trips out of the area were inoculated with protective preparations before leaving the base.<sup>10</sup>

In April 1944, a case of plague occurred in an arsenal guard who had been occupying a guardpost adjacent to the crowded harbor area. Despite the quarantine of the arsenal area and attempts at disinfestation, six additional workers in the arsenal had caught the infection by 15 May, and by the middle of the summer, the incidence had reached alarming proportions.<sup>11</sup> The outbreak from April to November consisted of 567 cases, 91 percent of which were fatal. All patients, except one Syrian and three French Europeans, were native Negroes. Rapid expansion of the population due to the war brought about extreme congestion, and since there were no sanitary facilities, infestation with vermin, rats, and fleas was universal. Crowded housing conditions, daily intimate contact at the markets, and visiting were conditions ideal for transmission of the infection. It was suspected, but not conclusively proved, that the human flea *Synosternus pallidus* Taschenberg was the main plague vector, since the number of *X. cheopis*, the natural suspect, was quite negligible in native huts and villages.<sup>12</sup>

International quarantine measures at the port were invoked by the French in the form of precautions against movement of rats from ships in the harbor. The U.S. troops in the area had been inoculated with the Army prophylactic against the infection. By 6 June 1944, it was necessary for Army medical officers to declare the entire city "off limits" for U.S. personnel. Americans entering the area on essential business were required to wear protective clothing sprayed with a flea repellent. All native employees were inoculated with the avirulent E.V. vaccine and were required to live on the post and to dust their clothing and their homes with DDT powder. Those working at the U.S. Army hospital were quartered in the compound and were required to bathe and change clothes before work. Homes and offices of all U.S. personnel and various contract companies were treated with DDT.

The general control measure used by the French health authorities was disinfestation of the houses and yards of infected patients. Cresol solution

<sup>10</sup> (1) Letter, Capt. Everett W. Ryan, MC, Headquarters, South Atlantic Wing, Air Transport Command, to the Surgeon, U.S. Army Forces, South Atlantic, 5 July 1943, subject: Bubonic Plague Epidemic at Dakar. (2) Memorandum, Col. S. Bayne-Jones, MC, Acting Director, Preventive Medicine Division, Office of the Surgeon General, for Col. Paul C. Gilliland, Surgeon, Air Transport Command, 14 Sept. 1943, subject: Plague Vaccination in Dakar and Marrakesch.

<sup>11</sup> Lewis, P. M., Buehler, M. H., and Young, T. R.: Plague in Dakar. Bull. U.S. Army M. Dept. 87: 13-16, April 1945.

<sup>12</sup> Kartman, L.: On the DDT Control of *Synosternus pallidus* Taschenberg (*Siphonaptera, Pulicidae*) in Dakar, Senegal, French West Africa. Am. J. Trop. Med. 26: 841-848, November 1946.



to kill both infected fleas and bacilli was sprayed from a firetruck carrying a tank of the solution. Next, the house and the adjacent structures were sealed and fumigated with chloropicrin gas. Rat burrows and debris piles were destroyed with sulfur dioxide. This program was supplemented by assistance from the Americans who dusted homes and as many natives as possible with 10 percent DDT powder in pyrophyllite.

These focal or spot measures proved to be inadequate. The French medical authorities thought that a greater increase in the incidence of the disease had been prevented, but the Americans thought that only a comprehensive program, encompassing at least all of the native sections of the city, could control plague.

Late in October, after some delay, an expanded program was instituted: Médina, the native suburb was divided into zones and surrounded by a cordon of 200 to 300 gendarmes. "Outlet stations" were established, and all persons leaving this area were dusted with 10 percent DDT dust. Inner cordon blocks enabled the dusting crew to dust the remaining people house by house; it was felt that this system covered nearly 95 percent of the population (about 125,000 persons). Simultaneously with the dusting of people, treatment of the floors, lower walls, and beds of the homes, public buildings, and meeting places with 5 percent DDT spray in kerosene was undertaken. Subsequent extensive surveys showed that the flea population had been greatly reduced. Of 316 houses found infested before spraying, all but 7 were completely free of fleas 2 weeks after treatment.

Entomologic observations on the lethal action on fleas of 5-percent solution of DDT in kerosene corroborated the field studies at Dakar. Where this material was sprayed on floors in concentrations of 100 mg. per square foot, the biting activity of adult fleas was inhibited within 10 minutes. The residual effect of both 10 percent DDT powder and 5 percent DDT in kerosene applied to floors killed fleas for 64 days.<sup>13</sup>

Further observations on the control of rat flea *X. cheopis* with DDT have been reported. Rats were captured in buildings before and after they had been dusted with DDT. The flea index was 13.6 fleas per rat before dusting. One month after dusting it was 0.6; in two instances, it was only 0.2 and 0.5 fleas per rat, 4 months after dusting.

The large rat population was sampled during the outbreak, and of 10,500 rats caught in wire traps by the French authorities, 3,501 were examined in the laboratory. Infection was proved in 65 *R. norvegicus* and *Rattus alexandrinus* rats. Of interest is the fact that two dead cats in the area were found to be plague infected.

The French Health Service used trapping and gassing as a part of a general rat control program. Around American installations, the program included poisoning of rats. The use of rat poisons in the native sections was abandoned because of the danger to children and domestic animals. The

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<sup>13</sup> See footnote 12, p. 83.

standard procedure in rat campaigns in the Dakar area required that rats be caught alive and drowned in cresol to insure destruction of both fleas and rats. The French authorities held the opinion that, if rats were poisoned in appreciable numbers and their carcasses were not removed, the fleas would leave the rats and go to man as an alternative host. Consequently, the number of rats destroyed in Dakar during the outbreak was never very great. In the light of this attitude toward rat extinction, the presumed accomplishment through disinsectization assumes greater significance.

It is difficult to appraise the effectiveness of the control program in stopping and confining the plague outbreak in Dakar. The seasonal decline of the disease had already started prior to the dusting with DDT. The last two cases of plague occurred on 22 and 25 November. This strongly suggests that the number of infective vectors had declined naturally during October preceding the drastic control measures.

An intensive vaccination campaign, with the living attenuated strain E.V. from Madagascar, was embarked on by the French authorities. The vaccine was manufactured locally at the Pasteur Institute in Dakar. Over 180,000 natives and 20,000 Europeans were vaccinated. In many Europeans, injection of 1 ml. of this vaccine in the scapular region produced severe symptoms and local reactions with tissue slough at the site of inoculation. Among those vaccinated over a period of 15 days, about 5 percent of the total cases, the case fatality rate was 66 percent, in contrast to 85 percent in noninoculated natives.<sup>14</sup>

The French medical authorities, on the basis of experiences with small groups of intimate plague contacts, expressed the view that early use of sulfadiazine may serve as a prophylactic measure in future outbreaks. During part of this experience, sulfadiazine was administered in amounts of 20 gm. for adults and 6 gm. for children over a 3-day period. Before chemoprophylaxis was instituted, 19 contacts became ill with plague. After its use, the disease developed in only one.

### Egypt

An outbreak of potential worldwide significance began in 1940 in Port Said, universal port of call at the northern end of the Suez Canal.<sup>15</sup> A few cases of bubonic plague (1 in 1940, 12 in 1941) precipitated the usual control measures of that time, including vaccination of the entire Arab population, but their effectiveness was inevitably limited by the heavy traffic through the port. In 1942, probably for the first time, Port Said was the victim of pneumonic plague (9 cases). Diagnosis of "fever of undetermined origin" and terminal bronchopneumonia were made before the true nature of the disease was recognized.

In November 1943, a sizable outbreak of plague flared up in Suez. By the end of the year, the incidence had built up rapidly; 397 persons had plague,

<sup>14</sup> Rotman, C. M. H.: Bubonic Plague in Dakar. *J. Roy. Nav. M. Serv.* 31:155-158, July 1945.

<sup>15</sup> Townsend, S. L.: Plague (Bubonic and Pneumonic) in Port Said. *J. Roy. Nav. M. Serv.* 30: 25-29, January 1944.

of whom 290 died. The infection prevailed through the spring of 1944 and by the middle of February had added another 276 victims and another 155 deaths. The overall case fatality rate was 66.1 percent. There were additional cases in Port Said in April. In all, 1,581 cases were reported in the area during the winter of 1943-44.

A total of 658 U.S. Army personnel and civilians were within 3 miles of the epidemic area. They were inoculated with Army plague prophylactic, and the area where the cases were occurring was declared "out of bounds." Civilian workers were instructed in methods of rat poisoning with red squill and of trapping rodents and were told how to obtain the required material. The floors of the houses were sprayed with kerosene mixtures. Rat-breeding places were eradicated by pouring kerosene into the hole and by cementing the openings of the ratholes in houses.

During January, the Egyptian public health authorities efficiently executed the control program by isolating all contacts of patients with pneumonic plague and inspecting daily all contacts of patients and of persons found dead. In February, with the decline of the outbreak because of natural phenomena, such as a change in wind direction from the Red Sea to the desert and a mean rise in temperature above 80° F., enforcement of control measures was stopped.

On agreement with Egyptian authorities, Lt. Col. Thomas G. Ward, MC,<sup>16</sup> the Medical Inspector, Middle East theater, was instructed to study the outbreak. It was determined that the outbreak had been preceded by a rise in the *X. cheopis* index for *R. norvegicus* from 0.1 in October to 5.1 in November. *P. pestis* was detected in rats trapped or found dead. The *X. cheopis* index rose to 13.31 in early December and maintained a level of around 10.5 during the entire month, but declined to 3.40 during January. The *X. cheopis* index curve was remarkably correlated with the incidence curve of cases in the outbreak. However, as late as January 1944, there was serious discussion that the epidemic was not being caused by rat fleas because dead rats had not been found.

At first, the Egyptian public health authorities doubted that rat fleas caused the outbreak. Since they were unable to find *P. pestis* in the pools of fleas, they advanced the idea that the disease was spread by the human body louse *Pediculus corporis*. Lice were collected from the clothing of patients with and without positive blood cultures and were macerated and inoculated into guinea pigs. Results of examinations of many thousands of lice were entirely negative. When Kafr el Morur became infected, the U.S. Army group demonstrated plague in 16 of 37 dead rats and proved that pools of fleas collected from these rats carried *P. pestis*.

Important clinical and pathologic studies were made. The cardiac findings are particularly interesting. As a rule, in plague the heartbeats are faint and rapid. The first sound is almost always muffled and in many cases cannot be heard; in severe cases, early in the disease, it may be extremely difficult to

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<sup>16</sup> Report, Lt. Col. Thomas G. Ward, MC, Medical Inspector, Headquarters, U.S. Army Forces in the Middle East, to the Chief Surgeon, U.S. Army Forces in the Middle East, 31 Mar. 1944, subject: Epidemic of Plague in Suez, Egypt.



hear the heartbeat at all. The heart may be enlarged slightly to the right. With the rise of body temperature, the pulse becomes weak and thready, the systolic pressure falls, and the beat is difficult to hear. The muscle is extremely weak, and on several occasions, death ensued immediately after some physical exertion. The American investigators attribute these signs to the endotoxin of *P. pestis* and consider the cardiac injury to be primarily responsible for the higher death rate in patients over 45 years of age.

In 142 cases of plague which yielded positive blood cultures, no patients recovered. Bubonic plague was complicated by pneumonia due to *P. pestis* in 38 cases; only 4 recovered, a death percentage of 89.5. All 12 patients with primary pneumonic plague in the outbreak at Suez died. In the light of reports on meningeal plague, the finding of plague bacilli in the spinal fluid in several cases of septicemic plague is particularly significant. Since plague results in rapid death, the gross pathologic findings are few—the characteristic ones being widespread hyperemia, few petechial hemorrhages, and softening of the heart muscle.

Opportunity was afforded for treating 56 severely ill patients, bacteriologically proved to have plague, with sulfadiazine. Usually, the patients were treated in the first 5 days of the disease. Of this group, 20 died, giving a case fatality rate of 35.7 percent. Seven of the twenty died before they had received 24 hours of treatment with sulfadiazine. The Army medical officers cautiously expressed the view that sulfadiazine probably has definite value in the treatment of plague. The course of the disease in patients treated with 100,000 units of penicillin, given every 4 hours (50,000 intravenously and 50,000 intramuscularly), was not altered. The tentative conclusion was drawn in February 1944 that penicillin is of little value; only three cases of bubonic plague and eight cases complicated by septicemia were treated.

### Palestine

An outbreak of plague in the Levant area of Palestine in September 1944 developed 93 cases with 30 deaths and 38 cases with 15 deaths in 1945. This occurrence was considered a hazard sufficient to warrant preventive inoculation with Army prophylactic of U.S. Army personnel and declaring the area out of bounds. Beyond increasing emphasis on sanitary procedures, additional control measures were not employed.

### North African Coast

As part of a general increase in plague along the North African Coast that started in Ferryville in the autumn of 1944, a small outbreak of plague at Oran in 1945 attracted attention.<sup>17</sup> The first patient with plague was a dockworker

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<sup>17</sup> (1) Letter, Lt. Col. Samuel C. Ellis, MC, Surgeon, Headquarters, Mediterranean Base Section, to Commanding General, Mediterranean Base Section, 25 Jan. 1945, subject: Plague Situation in Oran. (2) Letter, Maj. Joseph W. Still, MC, Headquarters, Mediterranean Theater of Operations, U.S. Army, to the Surgeon, Mediterranean Theater of Operations, U.S. Army, 31 Jan. 1945, subject: Investigation of Pneumonic Plague in Oran.

who died on 6 January 1945 of an illness originally considered influenzal pneumonia with onset on 29 December 1944. In rapid succession, eight native dockworkers in close association with this patient contracted pneumonic plague. Direct spread by contact included two nurses and a priest attending patients in the hospital. Chemoprophylaxis, 3 gm. of sulfathiazole daily, was employed for 85 direct contacts who were maintained under guard during the period of observation and treatment. Only one became ill, and he recovered.

This favorable result is particularly significant in that, for the first time at Oran, the time-honored, but rather distressing method of quarantining the contacts of pneumonic plague and weeding out those who fall ill was supplemented by chemoprophylaxis. In recent years, the value of such a prophylactic procedure has been amply proved. Sulfadiazine or sulfamerazine is preferred to sulfathiazole. The optimal dose and duration of chemoprophylaxis has not been established. The Oran experience suggests that larger doses of sulfonamides than those employed are in all probability desirable.<sup>18</sup>

Rodent control was part of the preventive program, although rodent plague was not found in the Oran outbreak. Rat trapping at strategic locations and examination of the rats for plague were instituted to determine the distribution of plague. DDT in kerosene was used liberally in buildings and living areas. Bedding, clothing, and persons of natives were dusted with DDT powder. United States military and civilian personnel were segregated from native dockworkers. Troops were restricted to post or isolated for appropriate incubation period before departure. Military personnel were reimmunized with Army vaccine. A small number of U.S. Army troops in the vicinity of Bizerte and Ferryville, Tunisia, were inoculated against plague when cases were reported in the local civil population during the latter part of 1944. Other control measures, including port quarantine procedures, were effected by the U.S. Navy and British forces.<sup>19</sup>

In July 1945, an outbreak of plague, both bubonic and septicemic, limited to two natives and one European, appeared in Casablanca. The first patient was a French employee in a warehouse of the port area where dead rats had been seen. American soldiers and personnel of the Italian service units were inoculated with U.S. Army plague prophylactic. Off limits restrictions were enforced for those who had not been recently inoculated. Entrance to the infected area was prohibited, except on essential business. By arrangement with the French authorities, a general rodent control program was preceded by extensive treatment with DDT powder, or DDT in kerosene was applied to warehouses, buildings, offices, trucks, and ships. Special attention was paid to protective clothing. These newly developed control measures limited the outbreak to a few cases and to a single week.<sup>20</sup>

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<sup>18</sup> Pollitzer, R.: Recent Trends in the Treatment and Control of Plague. *Acta Trop.* 6: 30-40, 1949.

<sup>19</sup> See footnote 17, p. 87.

<sup>20</sup> Essential Technical Medical Data, Headquarters, Africa-Middle East Theater, for July 1945, dated 31 Aug. 1945.

### Mediterranean Basin

Through rats, plague was reintroduced into Taranto, Italy,<sup>21</sup> Ajaccio, Corsica, and the island of Tenerife in the Canary Islands during the war.

Corsica had been free of plague until 1945, when between 11 May and 13 June there were 13 cases with 10 deaths.<sup>22</sup> The island was quarantined, and the entire population was inoculated with a protective preparation of killed bacilli, prepared by the Pasteur Institute. Two inoculations of 1 and 2 cc., respectively, were given at an interval of 8 days. Many thousands of rats were systematically destroyed by squill and by arsenic acid anhydride, and fleas were attacked with 5 percent DDT powder. The decline of the epidemic was attributed to sanitary measures and to the decrease in the number of fleas brought about by the change in weather.

Simultaneously with the reappearance of plague in the eastern Mediterranean, in the Suez Canal, and North African ports, more than 70 cases of human plague were reported from Malta. Observations made in this epidemic clearly indicate that toward the end of the war plague entered an expansive phase and was checked when greater vigilance was made possible by the cessation of hostilities.<sup>23</sup>

### China

Plague control was also a problem in the China and India-Burma theaters, and in the Pacific area, and was given serious consideration in planning for the occupation of Japan. The plague outbreak in Yünnan, southwest China,<sup>24</sup> became active in 1943.<sup>25</sup> This outbreak was of importance to the U.S. Army because the infected area lay astride the Burma Road.

The Yünnan Valley, a plague center since 1840 and even earlier, received the infection from Burma. Fanned by the Mohammedan rebellion of 1855, it is believed that plague progressed slowly, but inexorably from the border region of Yünnan to reach eventually Canton and Hong Kong and be distributed in 1894 to every continent in the world.<sup>26</sup> It was then, as it was in 1940, that war created a serious plague situation in Yünnan. While the region appeared free around 1908 and later, plague appeared in the city of Munginao in 1940, where a considerable epizootic broke out in February and March. A serious outbreak, definitely attributable to importation from Burma, developed between September and October 1943 in Lung-ch'uan. Direct and fairly frequented routes connect the towns with the notorious plague center of Bhamo (map 2). Transportation of rice from Lung-ch'uan in July to September led to the spread of plague into the Lo Pupa Valley and to Nan-tien in November 1944.

<sup>21</sup> Schulz, K. H.: Control of Plague in Taranto, Italy, 1945-46. An Account of a Successful Programme of Rodent Extermination. *Bull. World Health Organ.* 2: 675-685, 1950.

<sup>22</sup> Foreign Letters: Epidemic of Plague in Corsica. *J.A.M.A.* 130: 964, 6 Apr. 1946.

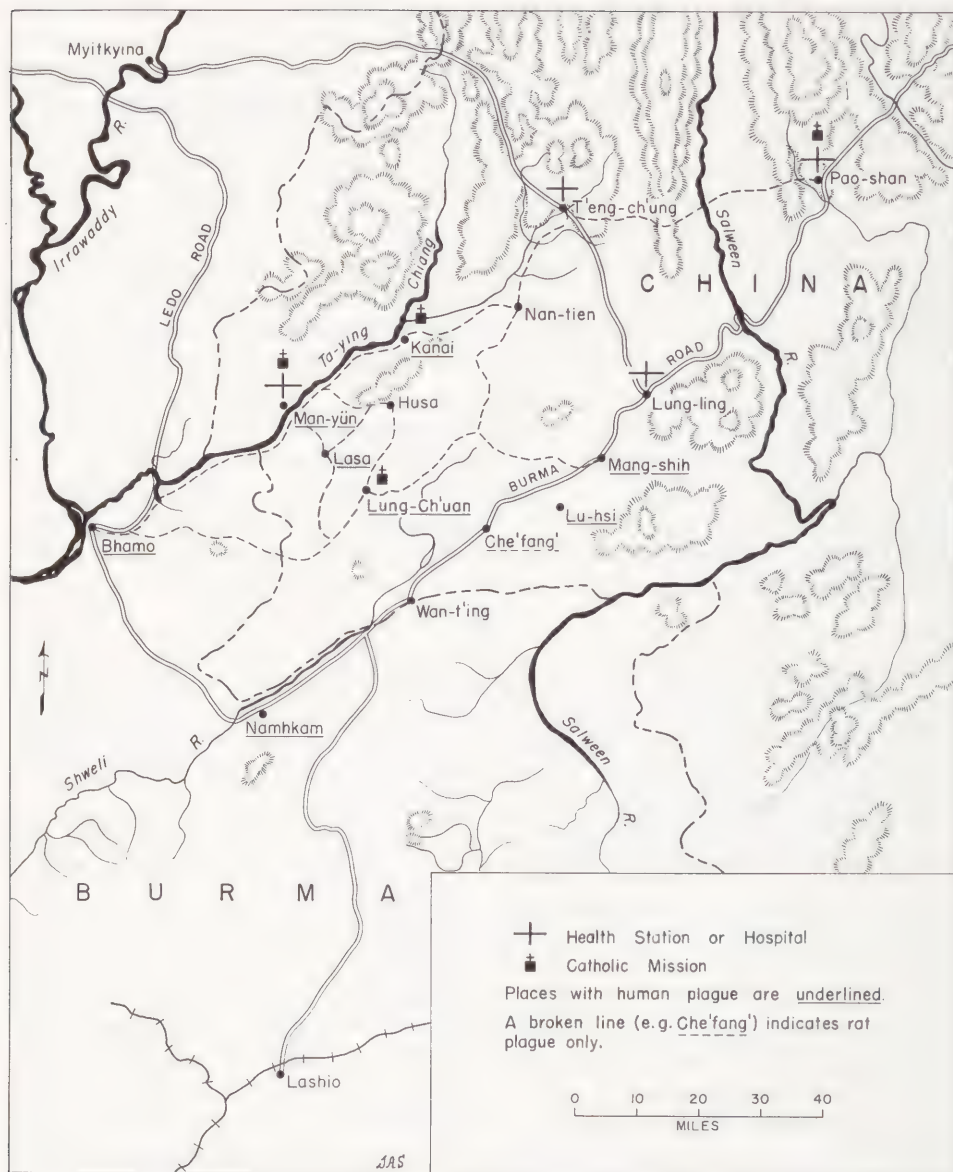
<sup>23</sup> Barnett, S. A.: Rat Control in a Plague Outbreak in Malta. *J. Hyg.* 46: 10-18, March 1948.

<sup>24</sup> UNRRA, Health Division. Plague Outbreak in Western Yünnan, China. *Epidemiol. Inform. Bull.* 1: 169-170, 28 Feb. 1945.

<sup>25</sup> Pollitzer, R.: Plague and Plague Control in China. *Chinese M. J.* 66: 328-333, June 1948.

<sup>26</sup> Meyer, K. F.: The Prevention of Plague in the Light of Newer Knowledge. *Ann. New York Acad. Sc.* 48: 429-467, 10 Apr. 1947.





MAP 2.—Human plague and rat plague in China and Burma.

Plague was also active in the Province of Fukien during World War II, with an estimated 8,279 cases. The adjoining Province of Chekiang had 2,085 cases. Both areas lie along the China Coast above Hong Kong and were in Japanese hands.

Since rats had become extraordinarily numerous in the Kanai [called Ying-kiang or Ying-chiang after 1935] area, it is not surprising that plague

appeared in that region between February and September 1943.<sup>27</sup> The rat epizootics were so severe that occasionally several hundred dead plague-infected rats were found in one compound. Under these circumstances, it was to be expected that the human outbreaks following the epizootic were often explosive. For example, in Nan-tien in June 1944, a family of 24 was affected following an epizootic; 17 contracted plague, of whom 9 died. In at least 80 of a total of 300 villages, the number of victims was estimated at 2,350 and deaths, at 1,350. During 1944 and 1945, various other regions in West Yünnan reported sporadic cases of plague, but accurate information is not available.

The greatest plague threat of the war to Americans came when U.S. troops entered North China. In anticipation of difficulties, a detailed program of control was formulated which included the desirable features of standard procedures and all of the additional measures derived from diverse experiences with plague by the Armed Forces in other parts of the world during the war.

In keeping with policies developed by the Preventive Medicine Service, The Surgeon General urged medical officers of the theater to cooperate with local and national governments to control the disease in the civil population in order to reduce the hazard to U.S. troops.<sup>28</sup> Control measures emphasized principally a rat campaign of traditional pattern readily adaptable to these regions. However, since the spread of plague at distance is due to transport of infected fleas, rather than to rodents, the outbreak in Yünnan smoldered for over 6 years, until the susceptible reservoir had apparently been exhausted.<sup>29</sup>

In the later stages of the outbreak, a large proportion of the population was inoculated with protective preparations containing killed plague organisms. In Nan-tien Village, 59 percent of the patients with plague were stated to have been inoculated with prophylactics prepared in China.<sup>30</sup> During the Kanai epidemic, the value of antiplague inoculation was considered worse than useless. Investigations disclosed that the inoculations were often carried out in places which already had had a very heavy rat mortality and human plague had already become rampant. Under these conditions, many of the inoculated fell ill and many of them died. However, most of these inoculated persons contracted the disease within 2 to 3 days after the first inoculation, having no doubt already been infected before they received the prophylactic. If, on the other hand, inoculations were given before rat infection had gained momentum, or better still before there had been any rat mortality, subsequent severe epizootics did not lead to epidemics, but at most to sporadic instances of human plague. Statistics attest to the considerably lower mortality among patients who had been inoculated than among those

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<sup>27</sup> See footnote 25, p. 89.

<sup>28</sup> Letter, Lt. Col. R. J. Carpenter, MC, for The Surgeon General, to Commanding General, U.S. Army Forces, China Theater, 7 Feb. 1945, subject: Plague in China.

<sup>29</sup> See footnote 25, p. 89.

<sup>30</sup> Pollitzer, R., and Chen, T. H.: Memorandum on Plague in West Yünnan, addressed to Dr. P. Z. King, Director-General, National Health Administration in Chungking, China, 1945.

who had not. Dr. Y. N. Yang's mortality figures were 14.4 percent among those inoculated with a preparation made under his direction, against 41.4 percent among the uninoculated. Furthermore, antiplague inoculation exerted a progressively greater influence on the therapeutic outcome as the number of inoculations increased. In the Kanai regions, sulfathiazole was used prophylactically, and it was reported that of the untreated 1,250 patients, only 100 recovered, while of the 1,000 treated, only 100 died. Only one of 27 who suffered plague died in Nan-tien following the prophylactic use of sulfadiazine.<sup>31</sup> Immunization and chemotherapy were apparently responsible for the low case fatality rate of 23 deaths (22 percent) among a total of 102 infected. These figures are significant in view of the recent confirmation that the mortality of the sulfonamide-treated immunized group was less than one-half of the fatality rate in the corresponding noninoculated group.<sup>32</sup>

In view of the plans for military operations in endemic areas along the eastern coast of China, all troops in the China theater were inoculated against plague early in 1945, and arrangements were made for reinoculation at 6 months' intervals.

Personnel assigned to bases in southern India were routinely inoculated against plague because of the endemicity of the disease in nearby villages. As a precautionary measure to protect troops operating along the Ledo Road, the surgeon of Advance Section No. 3, India-Burma theater, established a plague control organization, using specially qualified personnel from U.S. Army medical installations located in the area. This organization consisted of prevention and treatment teams prepared to go into action at the first sign of a plague outbreak.

## SUMMARY OF PREVENTIVE AND CONTROL MEASURES

Experience with the new insecticide DDT, developed during the war, has established the principle that attack on the flea is the desirable immediate objective in epidemic control, with attention to the rat as a long-term consideration. Preliminary observations on chemoprophylaxis as a preventive measure were particularly significant in the epidemic of pneumonic plague at Oran. These experiences permitted the planning and the adoption of a modern program of plague control.

The basic principle in modern control of human plague is direct attack on reported and recognized foci of infection, in contrast to the emphasis on stopping spread from the areas involved chiefly by quarantine and maritime sanitation, which are, however, still necessary measures. The essential steps taken are described under subsequent headings.

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<sup>31</sup> See footnote 30, p. 91.

<sup>32</sup> See footnote 18, p. 88.



## Preventive Measures To Be Instituted in Advance of Known Plague

All military personnel and as many civilians as possible in endemic areas should be inoculated with the most effective available plague prophylactic. Protection against infestation with fleas through the use of insecticide powder or repellents should be encouraged. Rodent survey and control programs should be initiated by medical unit commanders, preferably in cooperation with civilian public health agencies. The flea index of the rats should be determined. Trapped and dead rats should be examined for evidence of plague. To assure early awareness of the presence of plague, close medical intelligence must be maintained by unit surgeons and local military government and civilian public health authorities.

## Control of Sporadic and Endemic Plague

The recognition and early diagnosis of sporadic cases and confirmation by specific laboratory procedures are most important. All infectious material must be handled with greatest care and examined by experienced bacteriologists. Concurrent and terminal disinfection should be enforced. Patients should be isolated and strictest communicable disease techniques used. Attendants of patients with pneumonic or suspected pneumonic plague must wear hoods with goggles, coveralls or complete gown with trousers, and rubber gloves. Persons handling bodies of those who have died of plague should observe strict aseptic precautions. Contacts and suspected contacts of a patient with pneumonic plague should be disinfected and segregated for 7 days. Chemoprophylaxis for contacts is recommended—3 gm. of sulfadiazine (or sulfamerazine) per day for 5 days.

Area quarantine includes the enforcement of off limits regulations, traffic patrol, and disinfection of military personnel and civilians entering or leaving an infected area. Particular attention should be paid to refugees. The tendency of inhabitants to flee to the country and neighboring villages must be curbed, forcibly if necessary. Personnel departing from plague areas should be certified free from plague infection and from vermin infestation within 48 hours of departure.

Vessels in contact with ports in plague areas should be protected against entry of rats. Steps should be taken to assure that cargo taken on is free from rats. Rattrapping and poisoning should be continuous on vessels and they should be subject to inspection and fumigation, or both, by quarantine authorities in ports of entry in nonplague areas.

All U.S. military personnel within the general area should receive a stimulating dose of 1 ml. of plague prophylactic.

The most important control measure is directed toward the focal disinfection of houses and buildings where plague has occurred. Within a radius of 100 yards from the infected house, all persons, pets, domesticated animals, clothing, bedding, and furniture, rat runs and rat harborages should be dusted with DDT powder. Walls, ceilings, and floors of the houses should be treated

with DDT residual kerosene spray. When rattrapping leads to the discovery of plague in rats or of rats with a high flea index, disinfection should be extended and repeated. Personnel engaged in plague control should apply insect repellents to their exposed skin and clothing, including socks. Residents within or adjacent to a plague-infected area should be disinfested weekly with 10 percent DDT powder. Hospitals, barracks, messhalls, and storerooms of military installations and the quarters, clubs, stores, and common meeting places of foreign residents adjacent to a plague-infested area should be kept free of fleas by use of DDT powder or residual spray.

Rodent control measures—destruction of harborages and ratproofing measures—and rat extermination programs should be carried out as a sequent measure to focal disinfection. Rat extermination should include trapping, the use of poison, and fumigation.

Natives from towns and villages where plague is occurring should be inoculated against plague. The number of native employees within the military installation should be reduced to a minimum. Their quarters should be disinfested and each employee examined daily for fever and other evidence of plague.

### Control Measures of Plague in Epidemic Proportions

The measures to be used do not differ in kind from those required in the management of sporadic cases; with the exception that special case-finding teams are required. They make special epidemiologic studies of reported and suspected cases, initiate preliminary and emergency control measures, organize house-to-house surveys with the help of civilian personnel, assure inoculation and disinfection of all civilian personnel, and aid in providing adequate isolation measures for patients and civilian hospitals.

These teams are supported by others entrusted with disinfection and rodent control. Local disinfection of buildings and inhabitants, surveying the rat and flea population, rat extermination in the infected community and in nearby military establishments, and organization of facilities for disinfection by dusting at roadblocks are their functions. As an emergency measure a cordon sanitaire may be considered when plague is widely disseminated and provided natural barriers such as mountain ranges and rivers favor such a protective action. All general measures to limit the spread of infection are to be established promptly.

## RESEARCH

### Protective Inoculation Against Plague

The numerous attempts and experiments to perfect an immunizing preparation have been based on the observation that survival from clinical infection protects against a second attack, or at least transforms reinfection into a milder disease. Unfortunately, the epidemiologic and statistical records of the great plague epidemics furnish no accurate information concerning the degree of im-

munity enjoyed by individuals who recover from plague. This lack of dependable information has spurred the study of protective inoculation, which has continuously received attention since Haffkine conducted extensive animal experiments and tests on human beings with heat-killed broth antigen (from 1896 to 1897).

Study of the publications of the Indian Plague Commission and other Indian Government reports, particularly the summaries by Taylor,<sup>33</sup> and by Wayson, McMahon, and Prince,<sup>34</sup> makes it seem unquestionable that large and repeated doses of the Haffkine prophylactic frequently protects individuals against plague. However, it is equally well known that many inoculated persons, including even a number of those who had received more than one injection of the prophylactic, contracted the disease. By 1935, a questionnaire sent out by the Office International d'Hygiène Publique brought the general conclusion that there was little advantage in using antiplague antigens made from killed micro-organisms. The value of the Haffkine prophylactic was seriously questioned.

Research was then directed toward developing vaccines containing live avirulent organisms. Between 1932 and 1940, Otten in Java and Girard in Madagascar studied the benefits of this type of vaccination. But even a method of immunization utilizing live avirulent vaccines which, in the animal experiment, assures the best protection, when applied to man clearly shows its ultimate limitations. The reasons are: (1) the immunity after injection is short, offering no protection beyond 6 to 8 months; (2) one single subcutaneous vaccination does not protect against direct aerogenic infection; and (3) repeatedly revaccinated persons have died of plague contracted after natural exposure to this infection. Irrespective of these limitations, the Netherlands East Indies, the French colonies, South Africa, China, and Argentina turned their attention to antiplague vaccination with live avirulent vaccine. India, Egypt, and several other countries in the British Empire, however, favored the killed prophylactics.

This was the state of knowledge when the Subcommittee on Tropical Diseases, National Research Council Committee on Medical Research, on 22 October 1941 passed the following resolution: "Resolved that, even though the available knowledge does not seem to afford definite evidence of the benefits from the use of plague vaccine, it is considered advisable to vaccinate with killed plague bacilli of an approved strain all military or naval personnel under serious threat of exposure to bubonic plague."

In March 1942, the author (K.F.M.) and Dr. Newton E. Wayson submitted to the National Institute of Health a brief outline which served as a guide for the early manufacture of a formalin-killed agar-grown suspension of plague bacilli in saline. The selection of the strain of *P. pestis* to be em-

<sup>33</sup> Taylor, J.: Haffkine's Plague Vaccine. Indian M. Research Mem. No. 27: 3-125, March 1933.

<sup>34</sup> Wayson, N. E., McMahon, M. C., and Prince, F. M.: An Evaluation of Three Plague Vaccines Against Infection in Guinea Pigs Induced by Natural and Artificial Methods. Pub. Health Rep. 61: 1511-1518, October 1946.



ployed, the composition and preparation of the culture medium, and the methods for measuring the relative protective potency of the antigen vaccine were proposed as subjects to be investigated.

Through the years of tedious experimentation in search of a prophylactic inoculation against plague, the majority of workers had adhered to the principle that, if it can be shown that a preparation or fraction of *P. pestis* protects rats and mice or guinea pigs against an experimental infection, this is very good presumptive evidence of its efficacy in human beings. The early studies on plague vaccines conducted at the George Williams Hooper Foundation under contract with the Committee on Medical Research, Office of Scientific Research and Development, made use of this principle, but soon found that mice inoculated in two steps with 0.002 ml. of Army prophylactic resisted a challenge infection with 2,000 to 4,000 virulent plague bacilli, but that the prophylactic value was relatively little for guinea pigs. When used in the dose customary for human immunization (1.5 mg.=3,000 million organisms), only 10 to 20 percent of the guinea pigs survived a challenge infection with 500,000 plague bacilli.

In the course of extensive protection tests, different plague antigens were prepared from avirulent plague bacilli. Strains grown on agar or in liquid were killed by heat, by chemicals (formaldehyde, acetone at  $-70^{\circ}$  C., absolute alcohol, potassium sulfate, glycerol), and ultraviolet irradiation. Again, the immunogenic potency of these antigens was high for mice and rats, but relatively low for guinea pigs. The efficacy was enhanced by synergists such as aluminum potassium sulfate (alum) or aluminum hydroxide, but not by calcium phosphate. In some experiments, between 80 and 100 percent of the guinea pigs were immunized with an antigen which, in the unprecipitated stage, conferred protection to only 10 percent of the animals. The immunogenic potency was equally high when the antigens were incorporated in oil emulsions, but they produced severe inflammatory tissue changes at the site of injection.

These tests furnished convincing evidence that the degree of protection is raised when large and repeated doses of antigens are injected prophylactically. Furthermore, it is the actual mass of the bacterial protein, rather than the method of preparing the antigen from killed bacilli, that controls the immunogenic effect.

Chemical studies on virulent plague bacilli (Yreka strain) precipitated by acetone cooled to  $-70^{\circ}$  C., washed until free from water, and then dried in vacuo yielded on extraction with neutral sodium chloride solution at least two antigens. By precipitation at 0.33 saturation of ammonium sulfate at pH 7.0, a protein is readily obtained which crystallizes spontaneously in the form of fine needles upon cooling a solution supersaturated at  $40^{\circ}$  C. A second protein can be separated from the atoxic fraction. This protein contains carbohydrate, is soluble at 0.25 saturation, and precipitates at 0.30 saturation. These two atoxic proteins readily immunize mice, rats, and monkeys, but confer protection to guinea pigs only when incorporated in a water-oil emulsion. During the

later part of the war, these were recognized as the most important antigens in plague prophylaxis.<sup>35</sup>

Independently, but along similar lines, experimental work on plague prophylactics was carried out by the Laboratory for Plague Suppressive Measures of the U.S. Public Health Service.<sup>36</sup> During these studies, one of the workers accidentally contracted pneumonic plague, but recovered under sulfadiazine therapy. He had been inoculated repeatedly with Army plague prophylactic, with and without alum.<sup>37</sup>

In applying these observations to the prophylactic antiplague inoculation of man, indirect methods of measuring the response to the plague antigen were developed. Although the Army plague prophylactic stimulated agglutinins in low titers in about two-thirds of the injected human beings, this immune response was not considered significant. The protective value of the sera of the volunteers (Air Corps personnel and inmates at San Quentin prison) was therefore measured with the aid of a mouse-protection test.<sup>38</sup> With this relatively crude test, conclusive evidence has been secured that antigens (prepared with dead plague bacilli) with proved immunogenic potency for mice and guinea pigs stimulate, in approximately 70 percent of human volunteers, the appearance of weak protective antibodies. The observation that a third injection, or booster dose, definitely increases the levels of the protective antibodies is significant. There is distinct evidence that the prophylactic injection of killed plague bacilli (8,000 to 12,000 million) or of Fraction I antigen (2.5 mg.) assures both a higher percentage and a higher level of antibody response. The serum protective antibodies found in preliminary series of human inoculations with avirulent living plague bacilli were of a very low order. The few tests made furnished no conclusive evidence that avirulent living plague vaccines are superior to killed antigens when the appearance and the degree of serum antibodies is used as a measuring rod.

These experiments indicated that the much criticized method of antiplague inoculation which employs agar-grown killed antigens should prove effective provided the procedure is used before an outbreak of plague is in progress. Furthermore, the evidence is sufficiently encouraging to justify repeated inoculation of killed antigens as a means of enhancing the degree of protection. The immunity, though not absolute, nor even relative in some human beings, is nevertheless of undoubted value, since modern chemotherapy is more effective in the vaccinated. Prophylactic inoculations will serve as a supportive preventive measure in reducing the high case fatality rate in the course of plague epidemics.

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<sup>35</sup> See footnote 26, p. 89.

<sup>36</sup> See footnote 34, p. 95.

<sup>37</sup> Munter, E. J.: Pneumonic Plague. Report of a Case With Recovery. *J.A.M.A.* 128: 281-283, 26 May 1945.

<sup>38</sup> Meyer, K. F., and Foster, L. E.: Measurement of Protective Serum Antibodies in Human Volunteers Inoculated With Plague Prophylactics. *Stanford M. Bull.* 6: 75-79, February 1948.

## Chemoprophylaxis and Therapy of Plague

The comparative curative efficiency of 23 sulfonamides was evaluated by *in vitro* and *in vivo* tests. In order of their activity, the preparations are (1) very active compounds—sulfaquinoxaline, sulfapyrazine, sulfamerazine, sulfadiazine, and sulfathiazole—and (2) moderately active compounds—sulfacetimide, sulfacridine, sulfapyridine, and 4,4'-diaminodiphenylsulfone. The highly active sulfonamides—sulfapyrazine, sulfamerazine, and sulfadiazine—irrespective of dose, could not cure more than 30 to 40 percent of the infected animals when treatment was delayed and the drugs administered at a stage when the immunity mechanism had been damaged by the toxemia. At any stage of the infection and at any level of dosage, sulfadiazine proved statistically superior to sulfathiazole.

Since antiplague sera in combination with sulfonamides doubled the efficacy of each therapeutic agent, the Army assigned to two pharmaceutical companies the manufacture of potent antiplague sera, produced with the avirulent A1122 strain in rabbits. Immunization was extended over 16 weeks. The sera possessed a high agglutination and mouse-protection titer. By the application of newer methods of fractionation and concentration, globulin solutions with an agglutination titer of 1:10,240 and a mouse-protection unitage of 1,600 per milliliter were made available in a lyophilized form late in 1945. An opportunity was not afforded to test these sera on patients, but they served effectively in basic studies on the purification of the Fraction I antigen.<sup>39</sup>

In July 1944, Dr. Selman A. Waksman invited a study of therapeutic properties of streptomycin in plague. The George Williams Hooper Foundation proved that the antibiotic in amounts of 0.4 mg. per milliliter is bactericidal for different strains of *P. pestis* in 5 days. Advanced experimental bubonic plague in mice was readily cured with a total of 1,200 to 1,600  $\mu$ g. The remarkable bactericidal action of streptomycin was best demonstrated in experimental pneumonic plague in mice and guinea pigs. These preliminary observations on this most promising drug have since been fully confirmed. Streptomycin has now been proved in the successful treatment of at least 25 cases of human pneumonic plague.<sup>40</sup>

## SUMMARY AND PROPOSALS

The fact that no one in the U.S. military forces contracted plague during World War II, despite potential exposure in the Mediterranean area and the Orient, speaks of the efficiency of the cooperative measures taken by the Medical Department of the U.S. Army and the civilian public health departments. Al-

<sup>39</sup> Meyer, K. F.: Final Report to U.S. Public Health Service [January-June 1946], subject: Chemotherapy, Plague Vaccines, Anti-infectious and Antitoxic Properties of Antiplague Sera.

<sup>40</sup> (1) Quan, S. F., Foster, L. E., Larson, A., and Meyer, K. F.: Streptomycin in Experimental Plague. *Proc. Soc. Exper. Biol. & Med.* 66: 528-532, December 1947. (2) Meyer, K. F., and Quan, S. F.: Plague. In *Streptomycin: Nature and Practical Applications*. Baltimore: Williams & Wilkins Co., 1949, pp. 394-407. (3) Ghosh, P. K.: An Outbreak of Plague in an Epidemic Form Treated With Streptomycin and Sulfadiazine. *Indian M. Gaz.* 85: 441-445, October 1950.



though plague certainly presented a real threat in some areas, demanding considerable effort of medical officers, it did not interfere with military operations in any major way.

Some scientific advances made during the war brought about significant changes in the approach to control of plague and undoubtedly favorably influenced its success. Two of these were most important: The development of an insecticide (DDT) effective against the vector, the flea; and the development of agents that are useful not only for treatment, but more significant from the epidemic standpoint, for prophylaxis. These chemical agents altered the general plan in the following ways: The flea replaced the rat as the main target in sanitary measures; effective chemotherapy and prophylaxis improved quarantine and preventive policies; and sulfonamides, particularly sulfadiazine, were given to segregated contacts and offered them protection against the infection. These measures offered the civilian population an inducement to seek treatment, rather than to conceal cases—long a snarly problem in control. Since the development of the antibiotics, particularly streptomycin, hope could be offered for the first time in cases of pneumonic plague.

Contributions were made to the fundamental concepts of immunization against plague through the full support and interest of the Preventive Medicine Service, Office of The Surgeon General. Antigens were studied and purified and a prophylactic was prepared which, according to tests developed during the war, is definitely immunogenic if administered repeatedly. Although this preparation has not yet had extensive field trial, there is no reason to doubt that it enhances the antibacterial forces in the body sufficiently to warrant its use. Immunization has not been dimmed by chemoprophylaxis. Prophylactics prepared in India and China that have had field trial have lowered the attack and mortality rates, though not with any overwhelming success. They offer the inoculated better chance for recovery when they are treated with the sulfonamides or the antibiotics, or both, preferably early in the course of the disease. Inoculations with plague antigens offer a practical approach to lowering the attack rate in endemic areas.

In approaching the problem of epidemic plague as a whole, on a long-term basis, in addition to the application of the superior control measures now available, the U.S. Army should encourage and support research and inquiries into the following phases of plague control:

1. Evaluation of the newer rodenticides and insecticides, both on rats and wild rodents, with special reference to the disinfestation of materials capable of conveying infection.
2. Appraisal of the therapeutic value of the newer antibiotics—Chloromycetin (chloramphenicol), Aureomycin (chlorotetracycline), Terramycin (oxytetracycline)—in the treatment of bubonic and pneumonic plague.
3. Further evaluation of the sulfonamides or the antibiotics, or both, suitable for oral administration in the prophylaxis against plague, particularly the bubonic type.

4. Inquiries into the physiology of plague intoxication and the value of antiplague serum.

5. Comparative evaluation of the immunity offered to man by chemically killed detoxified plague bacilli, plague antigens such as Fraction I and living attenuated plague bacilli preserved in convenient form for extended transportation.

In particular, the importance of the multiple, versus the one-dose, use of prophylactics with and without adjuvants should be determined on human volunteers by serologic and mouse-protection tests.

## CHAPTER VIII

# Relapsing Fever

*Henry S. Fuller, M.D.*

## INTRODUCTION

The relapsing fevers are acute specific infections caused by spirochetes of the genus *Borrelia*, some of which are transmitted by the human body louse, *Pediculus humanus corporis*, while others are transmitted by certain species of the tick genus *Ornithodoros*. In a given situation, the vector is a most important factor in determining the epidemiology of the disease. Thus, louse-borne relapsing fever tends to be an epidemic disease whose incidence, where seasonal, corresponds to increases in the population of human body lice and whose mode of maintenance during interepidemic periods has not been clarified. On the other hand, tickborne relapsing fever, sometimes called endemic, occurs sporadically in human beings, with occasional large outbreaks, and is typically a place disease related to foci where, more or less frequently, human beings may make effective contact with infected ticks. The infection is actually enzootic among the ticks.

Wherever lousiness exists, epidemic relapsing fever is a problem of potential military importance. Under conditions of unusual degree of contact between susceptible troops and infected ticks, the tickborne infection may be of military importance, although usually to a lesser extent.

During World War I, relapsing fevers were apparently of no importance to U.S. troops. It is well known, however, that during and after that war, louseborne epidemics occurred among certain military as well as civilian populations; examples in Serbia<sup>1</sup> and in the Middle East<sup>2</sup> have been described; and statistics on case incidence have been published.<sup>3</sup>

At the beginning of World War II, the methods of prevention of transmission and spread of human lousiness and of louseborne diseases, in general, were well known to military medical personnel. The great advance in this respect during the war was the widespread and effective use of the residual insecticide, DDT, as a preventive measure applied to military and civilian

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<sup>1</sup> Hunter, W. : The Serbian Epidemics of Typhus and Relapsing Fever in 1915. *Proc. Roy. Soc. Med. (Sect. Epidemiol.)* 13 : 25, December 1919.

<sup>2</sup> Willcox, W. H. : Typhus and Relapsing Fever in Mesopotamia and Northern Persia. *Proc. Roy. Soc. Med. (Sect. Med.)* 13 : 59, May 1920.

<sup>3</sup> Trend of Relapsing Fever in European Area and Equatorial Africa. *Epidemiol. Information Bull.* 1(11) : 488-491, 15 July 1945.



populations alike.<sup>4</sup> Its use by the British in the course of an epidemic of louseborne relapsing fever among civilians in Kenya has been described.<sup>5</sup> Specific vaccines were and still are unavailable. Although, at the beginning of World War II, arsenical preparations were thought to be fairly uniformly effective in the treatment of human cases and in the prevention of recurrences, studies of certain series of cases have called this view into question. In addition to providing clinical material for further study of arsenical therapy, events during World War II revealed the potentialities of penicillin as a specific antibiotic in relapsing fever.

The experience of the U.S. Army Medical Department with regard to relapsing fever during World War II is here considered in relation to the problem as a whole.

## INCIDENCE

No deaths were reported as due to relapsing fever during World War II in the U.S. Army. Data on incidence of the disease, shown in table 19, were obtained from sample tabulations of individual medical records and, in general, should be interpreted as approximations rather than exact numbers.

TABLE 19.—*Incidence of relapsing fever in the U.S. Army, by area and year, 1940-45*

[Preliminary data based on sample tabulations of individual medical records]

Area	1940-45	1940	1941	1942	1943	1944	1945
Continental United States.....	29	0	1	3	10	10	5
Overseas.....	143	0	0	7	31	60	45
Total.....	172	0	1	10	41	70	50

In view of the small number of cases of relapsing fever in U.S. Army personnel during World War II, it is virtually impossible to establish trends of the disease, and any actual seasonal incidence would be liable to considerable distortion by the occurrence of a localized outbreak. An example of one such small outbreak is that described by Taft and Pike,<sup>6</sup> comprising 11 of the 29 cases reported for the United States.

Inasmuch as available factual data are quite fragmentary, it appears desirable to discuss relapsing fever with reference to geographic areas where particular problems arose: United States, Panama Canal Department, European theater, Africa-Middle East, and, finally, the China-Burma-India theater.

<sup>4</sup> Wheeler, C. M.: Control of Typhus in Italy 1943-44 by Use of DDT. *Am. J. Pub. Health* 36: 119-129, February 1946.

<sup>5</sup> Garnham, P. C. C., Davies, C. W., Hensch, R. B., and Timms, G. L.: An Epidemic of Louse-borne Relapsing Fever in Kenya. *Tr. Roy. Soc. Trop. Med. & Hyg.* 41: 141-170, September 1947.

<sup>6</sup> Taft, W. C., and Pike, J. B.: Relapsing Fever. Report of a Sporadic Outbreak, Including Treatment With Penicillin. *J.A.M.A.* 129: 1002-1005, December 1945.

## United States

A localized outbreak of tickborne relapsing fever was studied by Taft and Pike. The outbreak, occurring in northern Texas, gave rise to 11 proved cases treated in the Army Air Forces Regional Hospital, Sheppard Field, Wichita Falls, Tex. In discussing the clinical aspects of the disease in these patients, the authors emphasize the difficulties in diagnosis, the unusual incidence of neurologic involvement, and the relative ineffectiveness of Mapharsen (oxophenarsine hydrochloride) as contrasted with the striking response to penicillin therapy. Their particularly valuable clinical discussion should be consulted in the original article. Five of the group developed rashes on the second or third day following termination of the first febrile episode, and the finding of spirochetes during the afebrile period in a biopsied skin lesion is of special interest. The long course of the disease, marked by relapses on ineffective therapy, and the protracted convalescence, all associated with profound asthenia, indicate the potential loss in man-hours which might be incurred in an outbreak of larger proportions. Special attention should be paid to the observation that penicillin, in proper dosage, is effective in treatment of the acute episode, as well as in reducing the period of disability from the disease to a minimum.

Epidemiologic studies of this outbreak revealed that the men involved had slept on the ground, during a night exercise, in an area where many specimens of the tick *Ornithodoros turicata* were subsequently found living in the burrows of terrapins, *Terrapene ornata*, and in those of small mammals. The symptoms of illness began 6 or 7 days after the men were exposed in this area. From ticks on "prairie dogs" (a name applied rather indiscriminately to ground squirrels, as well as to *Cynomys* species) taken in this area, spirochetes were later recovered in experimental animals.

It may be noted that cases of tickborne relapsing fever have occurred in many localities in Texas, including Wichita County,<sup>7</sup> as well as in nearby Kansas. *O. turicata* (Duges) is the only known vector to man of relapsing fever in portions of Kansas, Oklahoma, and Texas, and it accepts a wide variety of hosts, particularly burrowing vertebrates.<sup>8</sup> The correct name for the spirochete transmitted by this tick is *Borrelia turicatae* (Brumpt), not *Borrelia recurrentis* of Taft and Pike. Evidence that the tick may act as a spirochetal reservoir has been provided by Davis.<sup>9</sup>

Fischer<sup>10</sup> reported the case of a man whose illness began during 1944 after return from field maneuvers where he slept on a mattress cover filled with

<sup>7</sup> Coleman, J. M., and Wright, H. E.: The Present Distribution of Relapsing Fever in Texas. In American Association for the Advancement of Science. Publication No. 18, Washington, D.C., 1942, pp. 26-28, A Symposium on Relapsing Fever in the Americas.

<sup>8</sup> Cooley, R. A., and Kohls, G. M.: The Argasidae of North America, Central America, and Cuba. American Midland Naturalist Monograph No. 1, 1944, pp. 1-152.

<sup>9</sup> Davis, G. E.: Relapsing Fever: The Tick *Ornithodoros turicata* as a Spirochetal Reservoir. Pub. Health Rep. 58: 839-842, May 1943.

<sup>10</sup> Fischer, I.: Penicillin Therapy in Relapsing Fever; Report of a Case. Am. J. Trop. Med. 26: 483-488, July 1946.

Spanish moss while camping beside the Colorado River, Tex., 2 miles from Camp Swift. No further information is given concerning the area where infection was presumably acquired from a tick. The patient was observed at the Station Hospital, Camp Bowie, Tex., where diagnosis was confirmed by demonstration of the spirochetes. Response to penicillin therapy was prompt, and no recurrence was noted during the ensuing 10 weeks of observation.

### Panama Canal Department

Fourteen cases of relapsing fever among military personnel of the Panama Canal Department were recorded for the years 1942-45, as follows: 1942, 6 cases; 1943, 2; 1944, 2; and 1945, 4.

Cohen<sup>11</sup> described six cases occurring during the spring of 1942 in Army personnel treated in the 210th General Hospital, Panama, C.Z. Three of the patients belonged to one tactical unit, three to another. The men of one group had slept in native huts for a single night about 12 to 14 days before onset of symptoms. The probable time of infection of the others could not be fixed precisely, inasmuch as they had slept in native jungle huts on many occasions until 3 days prior to onset of illness; these three became ill within 24 hours of one another. Diagnosis was confirmed in every case by the demonstration of spirochetes in preparations of blood. The benignity of the clinical courses of these men was consistent with previous observations of Panama cases. In spite of the finding of lice on two of the patients, Cohen's stated opinion is that "in view of existing evidence, it is more likely that the disease was tickborne." During 1945, four cases of relapsing fever were diagnosed by the demonstration of organisms in blood preparations, and each patient gave a history of tick bite incurred while visiting native dwellings.<sup>12</sup>

It should be emphasized that the proved tick vectors in this region are *Ornithodoros rudis* Karsch (synonyms: *Ornithodoros venezuelensis* Brumpt and *Ornithodoros migonei* Brumpt) and *Ornithodoros talaje* (Guérin-Ménéville). The studies of Dunn<sup>13</sup> also cited by Clark,<sup>14</sup> led to the belief that *O. rudis* is the principal vector of relapsing fever to man in tropical America and that, in Panama, *O. talaje* acts as an important agent in transmitting the spirochetes from animal to animal. Davis<sup>15</sup> pointed out, however, that it has not been shown experimentally that these two vectors are actually capable of transmitting each other's spirochetes. The correct name for the *Borrelia* transmitted by *O. venezuelensis* is *Borrelia venezuelensis* (Brumpt), of which *Borrelia neotropicalis* (Bates and Saint John) is a synonym. The spirochete transmitted by *O. talaje* must be regarded at present as unnamed.

<sup>11</sup> Cohen, A. G.: Relapsing Fever in Panama; Report of Six Cases. War Med. 7: 19-22, January 1945.

<sup>12</sup> Annual Report, Surgeon, Panama Canal Department, 1945.

<sup>13</sup> Dunn, L. H.: Observations on the Host Selection of *Ornithodoros talaje* Guern., in Panama. Am. J. Trop. Med. 13: 475-483, September 1933.

<sup>14</sup> Clark, H. C.: Relapsing Fever in Panama. In American Association for the Advancement of Science. Publication No. 18, Washington, D.C., 1942, pp. 29-34, A Symposium on Relapsing Fever in the Americas.

<sup>15</sup> Davis, G. E.: The Spirochetes. Ann. Rev. Microbiol. 2: 305-334, 1948.



The small total number of human cases simply means a low degree of effective contact between infected vectors and troops. Since man is merely an incidental host for ticks, playing no essential role in their maintenance or in the perpetuation of the tickborne *Borrelia*, he is an unreliable indicator of the amount of infection in nature. On the basis of the small number of cases occurring in troops in Panama, therefore, one is certainly not justified in drawing inferences as to the rate of infection in ticks in nature.

Preventive measures included indoctrination of personnel in the danger of visiting native habitations, particularly at night.<sup>16</sup>

### European Theater of Operations

According to Gordon,<sup>17</sup> during the course of operations in the European theater, only two cases of relapsing fever in U.S. troops were reported. One of these occurred in Great Britain and the other on the Continent. A patient who had been in Great Britain for some months before onset of symptoms was admitted to the 280th Station Hospital in August 1944 with a febrile illness which was diagnosed as relapsing fever when the spirochetes were found on dark-field examination and mouse inoculation of blood. The mode of infection was unknown in this instance, the patient giving no history of attack by ticks or lice. Inasmuch as the tick vectors are not known to occur naturally in this part of the world, one assumes that the infection was louseborne. Information concerning the other case is not available.

### Africa-Middle East

During the period from 1943 through 1946, a louseborne epidemic of relapsing fever involving several thousand persons, mainly civilians, spread through much of North Africa and Egypt. Epidemiologic background information concerning the outbreak is given by Stuart and by Gaud and co-workers.<sup>18</sup> During the period from September through December 1945, 10 cases were reported among U.S. troops at Casablanca, French Morocco.<sup>19</sup> The fact that the civilian epidemic did not become a military medical problem in the U.S. troops was probably related to efforts of military preventive medicine which, although aimed primarily against louseborne typhus, naturally included measures designed to prevent infestation with lice.

During the course of the epidemic in Egypt, members of the United States of America Typhus Commission observed and treated cases of louseborne re-

<sup>16</sup> Cox, W. C. (editor): The Prevention of Disease in the United States Army During World War II. The Panama Canal Department, 1 Jan. 1940 to 1 Oct. 1945, vol. II, p. 217. [Official record.]

<sup>17</sup> Gordon, John E.: A History of Preventive Medicine in the European Theater of Operations, U.S. Army, 1941-45, vol. I, pt. III, pp. 26-27. [Official record.]

<sup>18</sup> (1) Stuart, G.: Relapsing Fever in North Africa and Europe, 1943-45. Epidemiol. Information Bull. 1(11): 453-464, July 1945. (2) Gaud, M., and Morgan, M. T.: Epidemiological Study of Relapsing Fever in North Africa (1943-45). Bull. World Health Organ. 1: 69-92, 1947-50. (3) Gaud, M., Khalil Bey, M., and Vaucel, M.: The Evolution of the Epidemic of Relapsing Fever, 1942-46. Bull. World Health Organ. 1: 93-101, 1947-50.

<sup>19</sup> Essential Technical Medical Data, Headquarters, Africa-Middle East Theater, U.S. Army, for Dec. 1945, dated 12 Feb. 1946, inclosure 1 thereto.

lapsing fever occurring among the native population. In this connection, the observations of Zarafonetis and coworkers<sup>20</sup> are especially important. They confirmed and amplified the findings of previous investigators showing that sera of patients with louseborne relapsing fever may agglutinate *Bacillus proteus* OX-K. They pointed out that it is therefore necessary to interpret Weil-Felix OX-K results with caution in areas where both tsutsugamushi disease and relapsing fever are present. They further showed that relapsing fever does not appear to interfere with Weil-Felix OX-19 results, or with complement fixation tests using purified rickettsial antigens in the diagnosis of epidemic louseborne typhus.

During June and July 1944, five cases of relapsing fever in U.S. troops occurred in the Kazvin area, Persian Gulf Command.<sup>21</sup> Although the men gave no history of bites by ticks or lice, Argasid ticks were collected in buildings outside and inside the camp area. A report on their final identification is not available, but it is noted that dead ticks were found after barracks had been sprayed with 5 percent DDT in kerosene.<sup>22</sup> This author would point out that a known tick vector in this area is *Ornithodoros tholozani* (Laboulbene and Megnin), of which *Ornithodoros papillipes* Birula is a synonym.

### China-Burma-India

According to preliminary data based on sample tabulations of individual medical records, there were 70 cases of relapsing fever among U.S. Army personnel stationed in this area during 1942-45: 1942, 0; 1943, 4; 1944, 36; and 1945, 30. Surprisingly little information concerning these cases is available, and Blumgart<sup>23</sup> pointed out that it is virtually impossible to be certain that five cases reported from the India-Burma theater were actually relapsing fever. At least one officer was known to have reported recurrent malaria as relapsing fever. The majority of cases in U.S. troops apparently occurred in China, but information concerning them is scanty. Although louseborne relapsing fever was one of the most prevalent diseases noted among Chinese treated at the 22d Field Hospital, Chan-i, China, the only case among American personnel was that of the admission clerk who worked in close contact with sick Chinese soldiers.<sup>24</sup> One may speculate, therefore, that cases in the U.S. troops were probably louseborne, inasmuch as this type of spread is known to occur in China, and furthermore there were undoubtedly opportunities for contact with louse-infested Chinese civilians and troops.

<sup>20</sup> Zarafonetis, C. J. D., Ingraham, H. S., and Berry, J. F.: Weil-Felix and Typhus Complement-Fixation Tests in Relapsing Fever, With Special Reference to *B. proteus* OX-K Agglutination. *J. Immunol.* 52: 189-199, March 1946.

<sup>21</sup> Essential Technical Medical Data, Headquarters, Persian Gulf Command, U.S. Army, dated 19 Sept. 1944, and 18 Nov. 1944, inclosure 4 thereto.

<sup>22</sup> Letter, Capt. Manning A. Price, SnC, Malariologist, to Commanding General, Persian Gulf Command, 11 Nov. 1944, subject: Report of Malaria and Louse Control Activities for Month of October.

<sup>23</sup> Report, Col. Herrman Blumgart, MC, Medical Consultant, India-Burma Theater of Operations [about 15 Oct. 1945], subject: Relapsing Fever.

<sup>24</sup> Essential Technical Medical Data, Headquarters, U.S. Forces, China Theater, Rear Echelon, for March 1945, dated 27 Apr. 1945.

Owing to pediculosis of Chinese recruits and to the observed incompleteness of delousing measures as applied to these individuals in the Chinese Army, Chinese troops were a source of material for the clinical study of relapsing fever by U.S. Army Medical Corps personnel. The main problem concerned cases which developed in Chinese troops in India, shortly after these soldiers had been flown over the Himalayan "Hump" from K'un-ming. Occasional cases among Chinese who had been in India for several months did not constitute a serious health problem.

The 134 Chinese recruits treated in Assam by Wolff<sup>25</sup> showed, as a group, signs of malnutrition and multiple vitamin deficiencies as well as infection with intestinal nematodes. Diagnosis of relapsing fever was based on demonstration of spirochetes in blood preparations, inasmuch as the clinical picture had to be differentiated from several other febrile conditions frequently observed. Specific therapy consisted of two intravenous injections, each 0.04 gm. of Mapharsen, given 3 to 5 days apart. Convalescence was rapid following the use of Mapharsen, and recovery was apparently complete in a few days. Recurrences were noted in 13 percent of cases treated in this manner. Mortality in the 134 cases was 11.9 percent, which was lower than might have been expected in persons whose general health was already impaired when relapsing fever was contracted.

Dillon and Fischer<sup>26</sup> treated more than 250 cases of relapsing fever in Chinese troops whose nutritional status was poor and in whom the rate of infection with intestinal parasites was high. The overall mortality rate was 2.8 percent. Diagnosis was based on demonstration of spirochetes in blood preparations. Varying doses of neoarsphenamine were used for specific treatment of the infection. Because of low relapse rate, low mortality rate, absence of complications, and convenience of dosage, 0.3 gm. given intravenously was found to be the most appropriate dosage, on the basis of administration to 193 patients.

## CONCLUSIONS

It is important to evaluate the risk to troops operating in infected areas. In the absence of refined figures, comparisons of approximate figures for relapsing fever in civilians during the North African louseborne epidemic with approximate figures showing negligible rates in U.S. troops in the same area indicate the very minor risk to troops who are properly indoctrinated and protected against louse infestation or contact with lousy persons. The risk of sporadic cases or outbreaks of the tickborne disease is continually present in those habitats which harbor infected ticks. In the absence of any effective

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<sup>25</sup> Wolff, B. P.: Asiatic Relapsing Fever: Report of 134 Cases Treated With Mapharsen. *Ann. Int. Med.* 24: 203-216, February 1946. (Abstr.: *Bull. U.S. Army Med. Dept.* 4(2): 124-125, August 1945.)

<sup>26</sup> Dillon, J. A., and Fischer, W. J. H.: Observations on Relapsing Fever. *Field Medical Bulletin, Headquarters, Services of Supply, U.S. Army Forces, China-Burma-India*, vol. 3, No. 8, August 1944, pp. 92-95.



specific vaccine, prevention of human infection is based on avoidance of contact with infected lice or ticks.

Owing to the effectiveness of measures designed to prevent troops from attack or infestation by human body lice and by *Ornithodoros* ticks, relapsing fever was actually of minor importance among U.S. Army personnel during World War II. The main contributions of personnel of the U.S. Army Medical Department concerned specific therapy of the disease with various arsenical preparations and with penicillin.

## CHAPTER IX

# Sandfly Fever (Pappataci, Phlebotomus, Three-Day Fever)

*Marshall Hertig, Ph. D., and Albert B. Sabin, M.D.*

## Part I. History of Incidence, Prevention, and Control

*Marshall Hertig, Ph. D.*

### GENERAL CONSIDERATIONS

Sandfly fever is a short-term febrile disease of virus etiology transmitted by the bite of one or more species of sandflies of the genus *Phlebotomus*.<sup>1</sup> Although there are no fatalities and the victims are incapacitated usually for no more than 1 or 2 weeks, the disease is potentially of great military importance. This is because large numbers of men may be incapacitated at precisely the time when they are most needed. The danger would be especially great for invading forces which had not been previously exposed to the disease and would therefore be composed of nonimmune persons. The defending forces, whether composed of natives or troops who had been in the regions during the previous sandfly season, would be mostly immune. Since the incubation period is very short, a matter of only 3 to 6 days, it would be possible for the invaders to have a large fraction of their forces rendered noneffective in the first critical days of a campaign.

### Military History

Since armies, rather than resident populations, have been the chief, or at least the most spectacular and articulate, sufferers from sandfly fever, its history is very largely military. The classic investigations in Dalmatia on the etiology and transmission were made by an Austrian military commission consisting of Doerr, Franz, and Taussig.<sup>2</sup> Most of the later experimental work on the virus and its transmission has been performed under military auspices. Some of the first studies on the bionomics of *Phlebotomus*, carried out by various

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<sup>1</sup> War Department Technical Bulletin (TB MED) 82, 8 Aug. 1944.

<sup>2</sup> Doerr, R., Franz, K., and Taussig, S.: Pappataciefieber, ein endemisches Drei-Tage-Fieber im adriatischen Küstengebiet Österreich-Ungarns. Leipzig & Wien, Deuticke, 1909.

British investigators in Malta before World War I,<sup>3</sup> were stimulated by the severe problems of sandfly fever and sandfly annoyance in local military establishments. A large proportion of our epidemiologic information has come from experiences of British forces at military stations and during campaigns in the Mediterranean region, the Middle East, and in India.<sup>4</sup> Americans in general had had no experience with the disease before World War II.

The military importance of the disease in all cases has rested on the central fact that during the sandfly season newcomers could suddenly be rendered non-effective in great numbers. This has applied not only to newly arrived foreign troops but also to natives who came from regions where the disease did not occur. For example, Indian troops from certain hill regions have been as severely affected as the British. The military effects have ranged from interference with routine garrison duties and training schedules and temporary overcrowding of hospitals to ineffectiveness in combat. Sinton<sup>5</sup> gave an instance from the Waziristan campaign in 1917 where a battalion was attacked almost en masse by sandfly fever and rendered temporarily unfit for further service. He cited the reports of others that the disease was the cause of "a great deal of ineffectiveness among troops of the Mesopotamian Expeditionary Force" in World War I, and that it accounted for 50 percent of the cases of sickness among oversea personnel of the Royal Air Force. In Palestine during World War II,<sup>6</sup> the operation of air-training schools with very crowded schedules was seriously affected by the disease. The experience of the U.S. Army in World War II in which there were an estimated 8,500 cases of sandfly fever in the Sicily Campaign and potentially serious outbreaks on the Italian mainland is reported by Sabin (pp. 168-174).

### Epidemiology

**Distribution.**—Sandfly fever is limited chiefly to the Old World between latitudes 20° and 45° north. It extends from the Mediterranean to India and Burma and possibly to China. The following details as to distribution are quoted from Sabin, Philip, and Paul:<sup>7</sup>

The disease is definitely known to occur in Italy as far north as the Po Valley, Sicily, along the Adriatic coast of Yugoslavia as far north as the Istrian peninsula, Greece,

<sup>3</sup> (1) Birt, C.: Phlebotomus Fever in Malta and Crete. J. Roy. Army M. Corps 14: 236-258, 1910. (2) Newstead, R.: The Papataci Flies (Phlebotomus) of the Maltese Islands. Bull. Ent. Res. 2: 47-78, 1911. (3) Marett, P. J.: The Bionomics of the Maltese Phlebotomi. Brit. M.J. 2: 172-173, July 1915.

<sup>4</sup> (1) Sinton, J. A.: Indian Species of the Genus Phlebotomus; Role of Insects of the Genus Phlebotomus as Carriers of Disease, With Special Reference to India. Indian J.M. Research 12: 701-729, April 1925. (2) Anderson, W. M. E.: Observations on *P. papatasi* in the Peshawar District. Indian J.M. Research 27: 537-584, October 1939.

<sup>5</sup> See footnote 4(1).

<sup>6</sup> (1) Report, Lt. Col. Ross L. Gauld, MC, Epidemiologist, Epidemiology Section, 15th Medical General Laboratory, 6744 Medical Center (OVHD), to Commanding Officer, 15th Medical General Laboratory, 16 Oct. 1944, subject: Trip to Jerusalem in Connection With Sandflies and Sandfly Fever. (2) Report, Maj. Marshall Hertig, SnC, 15th Medical General Laboratory, 6744 Medical Center (OVHD), to Surgeon, North African Theater of Operations, U.S. Army, 12 Oct. 1944, subject: Trip to Jerusalem in Connection With Sandflies and Sandfly Fever.

<sup>7</sup> Sabin, A. B., Philip, C. B., and Paul, J. R.: Phlebotomus (Pappataci or Sandfly) Fever; A Disease of Military Importance; Summary of Existing Knowledge and Preliminary Report of Original Investigations. J.A.M.A. 125: 603-606, 693-699, July 1944.



Malta, Crete, Cyprus, Egypt, Palestine, Syria, Iraq, Persia (Iran), Crimea and the Transcaucasian region, and the northwest and central provinces of India. There are also reports which would suggest that this disease may occur in China as far north as Peiping and Tientsin and as far south as Hong Kong, in Burma along the coast of the Bay of Bengal, in Ceylon, in the Poona region of India, in Aden and along the adjacent Red Sea coast of Arabia, the Anglo-Egyptian Sudan, along the Mediterranean coast of Africa—particularly the eastern portion, Corsica, the Mediterranean coast of France, Gibraltar, and along the Atlantic coast of Portugal. Reports of a similar disease in countries lying just north or south of the Equator have come from Kenya and the Tanganyika Territory in Africa and from the region of Bolivar [Colombia] in South America. The disease is not known to occur in the United States.

In Panama, there occurs sporadically a short-term fever which is clinically similar to sandfly fever and which has at times been diagnosed as such.<sup>8</sup> However, the identity of this disease with sandfly fever has never been established nor, so far as known, has any experimental work with *Phlebotomus* and sandfly fever ever been undertaken in the Western Hemisphere. It may be remarked that in Panama there are a number of species of *Phlebotomus* which bite man. Their distribution is sufficiently wide and varied as to habitats to permit their consideration as vectors.

In the Pacific areas, cases of sandfly fever were reported but never confirmed by later investigation, as shown by Lt. Col. (later Col.) Cornelius B. Philip, SnC (pp. 123–124). Sera from a number of cases were shipped to the United States and inoculated into volunteers. Sera from the Philippines gave only negative results, while from the New Guinea specimens four strains of typical dengue were recovered.

The occurrence of sandfly fever in the Western Hemisphere and in the Pacific remains unproved.

**Symptomatology and diagnosis.**—Clinically, the disease is characterized by sudden onset, fever lasting usually about 3 days (whence the name 3-day fever) ranging from 100° to 105° F., with severe frontal headache, pain in the eyes, photophobia, pain in the back and joints, and general malaise. The disease may simulate influenza, other respiratory infections, the initial stages of other febrile diseases, and may be confused with dengue. From the latter, it may usually be distinguished by the absence of a rash and the shorter febrile period.

A decrease in the number of segmented neutrophils together with a relative and absolute increase of immature neutrophils is a phenomenon shown by Sabin and others (p. 110) to be constant in sandfly fever and an important aid in diagnosis.

There is no distinctive sign or specific test, and, as a result, diagnosis is often difficult, particularly under field conditions. The practical implications are illustrated by the Army's experience in Sicily where many undiagnosed febrile cases, which were undoubtedly sandfly fever, were treated as malaria and needlessly evacuated to North Africa (pp. 168–174).

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<sup>8</sup> Cheney, G., and Azanzaz, G.: The Identification of Tropical Fevers of Virus and Rickettsial Origin. Stanford M. Bull. 4: 104–116, August–November 1946.

**Immunity.**—Native populations are seldom affected severely by sandfly fever. Indeed, the people may hardly be aware that there is such a distinct disease entity, even in an area capable of producing an epidemic among newcomers. This was the case in Naples in 1944 (p. 121). The scattered cases which were found among civilians by systematic search had been attributed to colds and the like and had not been deemed worthy of medical attention. Infection is obviously acquired during childhood, with a considerable degree of resulting immunity which is renewed from time to time by subsequent infections. From the readiness with which newcomers may contract the disease in the absence of any recognized outbreak among the local population, it is evident that opportunities for reinfection of the latter are a more or less constant feature of the epidemiology.

The duration of the immunity in an adult from a single attack has been shown experimentally by Sabin and others to be at least 4 months and even as long as 2 years (p. 148), but that it may have disappeared after 4 to 7 years. In any case, it appears that the immunity from a single attack and from whatever reinfections may occur naturally is such that troops who remain in the same area are, like the local civilians, little troubled by sandfly fever. However, reports of second attacks in the same season nearly always have been associated with a change of station. A reasonable explanation for such repeated attacks is provided by the demonstration that there are at least two immunologically distinct strains in the Mediterranean area; namely, the Sicilian-Middle East strain recovered in 1943, and the Naples strain recovered in 1944 (pp. 165–166).

**Criteria for the identification of the virus.**—Sabin has pointed out that the ultimate criterion for the identification of a given strain of virus, as that of sandfly fever, is the actual demonstration of its transmissibility by *Phlebotomus* (p. 132). This was done in the case of the Middle East strain. A procedure of this sort is possible only under certain special conditions. It was not feasible in the case of the Naples virus, but there remains no reasonable doubt that it was sandfly fever. Clinically and epidemiologically, it followed the classic pattern, and it was amply shown by competent observers to be associated with *Phlebotomus papatasi*. In practice, in the face of an outbreak of what appeared to be sandfly fever, control measures would, of course, be instituted as soon as possible. There would be neither necessity nor justification to await the definitive demonstration of transmission by *Phlebotomus*.

The following seem to be reasonable grounds for assuming a given outbreak to be sandfly fever and for proceeding on that assumption with whatever control measures are feasible:

1. Correspondence with symptomatology and clinical course of sandfly fever.
2. Occurrence during the sandfly season in a known endemic area.
3. Occurrence in newcomers, with the local population apparently unaffected.

4. Demonstrated association with *Phlebotomus*, especially *P. papatasi* within its range: Sandflies found in fair abundance either in the act of biting at night or at rest in living quarters during the day. It would usually be possible to demonstrate the converse; namely, that specific quarters, barracks, or localities with little or no disease had few or no sandflies, or at least that *P. papatasi* was scarce or absent.

5. Prompt cessation of the outbreak on the application of control measures, such as residual DDT (p. 121).

### Etiology and Transmission

Doerr and others (p. 109) working on the Dalmatian coast in 1908, showed that the etiologic agent was filterable, that blood taken from patients on the first day could produce the disease when inoculated into other persons, and that the disease could be transmitted by *P. papatasi*. These basic facts have been confirmed by a number of later investigations<sup>9</sup> in the Mediterranean, India, and Transcaucasia. No insect other than *Phlebotomus* has been shown capable of transmitting the infection, and no animal other than man is known to be susceptible.

**Insect vector.**—*P. papatasi* is the species with which all recorded experimental infections have been accomplished and is the species which has been found associated with the disease in those areas where sandfly fever has been most studied. *P. papatasi* is one of the most widely distributed species of the genus and occurs in an extraordinary variety of habitats from the Mediterranean to the western half of India (fig. 4). Around the Mediterranean littoral, it is found, often in great abundance, in rural areas as well as in the heart of large cities, such as Naples and Athens. In the salt desert around the Dead Sea, this species occurs in enormous numbers even at some distance from human habitations. In certain semidesert regions of Turkmenistan, it has been found breeding in the burrows of rodents. The possibility that other species of *Phlebotomus* may also be vectors has not been investigated experimentally. Outside the range of the *P. papatasi*, for example, in Burma and China, if the reported disease is actually sandfly fever, other species must necessarily be involved.

**Life history.**—The breeding places of *P. papatasi* are in moist, loose soil in dark, humid, sheltered places such as those beneath stones, in masonry crevices, in deep soil cracks, or in animal burrows. The female secures a blood meal and after several days lays a batch of eggs, a process which may be repeated several times. The males do not suck blood. The eggs hatch in about 10 days. The larvae are scavengers and feed on insect or animal feces, decaying

<sup>9</sup> (1) See footnote 3(1), p. 110. (2) Whittingham, H. E.: The Etiology of *Phlebotomus* Fever. J. State Med. 32: 461-469, September 1924. (3) Shortt, H. E., Poole, L. T., and Stephens, E. C.: Sandfly Fever on the Indian Frontier; A Preliminary Note on Some Laboratory Investigations. Indian J.M. Research 21: 775-788, April 1934. (4) Moshkovsky, S. D., Demina, N. A., and others; Sandfly Fever. VIII. Transmission of Sandfly Fever Virus by Sandflies Hatched From Eggs Laid by Infected Females. Med. Parasitol. (Moscow) 6: 922-937, 1937. Abstract in Trop. Dis. Bull. 41: 565, July 1944.





FIGURE 4.—Stone walls, Algeria. Typical resting and breeding places of *Phlebotomus*.

vegetation, or other organic debris. The larval development usually takes from 2 to 4 weeks, and the pupal stage requires another week or 10 days. The whole life cycle normally takes at least 6 to 8 weeks. Overwintering occurs in the last (fourth) larval stage. The sandflies begin to emerge about April and have largely disappeared by October or November. There is no evidence that adults can overwinter.

**Habits and flight range.**—The adult sandflies become active about dusk and may feed at any time during the night, seeking shelter by morning. The flight is silent, which is reflected in the name *pappataci*, a word of Italian derivation said to mean “bite, say nothing.” They are able to pass easily through ordinary screening or mosquito netting. Contrary to repeated statements, they may be found on the upper floors of buildings, from 50 to 70 feet above ground level. *P. papatasi* tends to remain in rooms where it has fed and may often be found in great numbers in the upper corners.

The flight range of *P. papatasi*, in common with that of sandflies in general, is very short, usually a matter of only 100 meters or thereabouts from their breeding places. This at times leads to extreme local spottiness of distribution, so that certain sections of town, or groups of houses, or even certain rooms may be heavily infested while there are few sandflies in the immediate surroundings. The peculiarities of local distribution depend on the availability of potential breeding places and of daytime shelters, and to a certain extent on the prevailing winds and local air currents. An exception to the normally

short flight range has been noted in desert habitats, where with marked sandflies a range of 1,500 meters has been measured.

Sandflies have often been kept alive in the laboratory for several weeks, and it is supposed that this reflects their longevity in nature. With suitable technique, they can be fed repeatedly in the laboratory, and it is known (from the state of the ovaries and the glands) that they commonly refeed at least once in nature, a point of importance in the transmission of a disease from person to person.

***Phlebotomus* and the virus.**—The experimental evidence indicates that sandflies may become infective about a week after they have fed on a patient, but the extremes of time required for the development of the virus have not been determined. Throughout the sandfly season, there are continuous opportunities for the transmission of the virus from person to person. Carrying the virus over the winter, however, has been more difficult to explain. The virus is circulated in the blood of man for only 2 or 3 days, and no other vertebrate host is known. Early in the study of the disease, it was suggested that the sandfly larvae might become infected either via the egg or by eating the dead bodies of sandfly adults and thus carry the virus through the winter. Certain investigators<sup>10</sup> have succeeded in transmitting the disease by the progeny of infected sandflies, while Sabin and others have failed.

In this connection, there occurs to the writer a point which he has not seen discussed; namely, that the experimental infection of sandfly progeny via the larvae may happen more readily with a generation which is actually destined to overwinter. *P. papatasi*, like other species of *Phlebotomus* in climates with a cold winter, exhibits the phenomenon of the diapause; that is, larvae from eggs laid toward the end of the sandfly season develop normally to the fourth instar but do not pupate until the following spring. This phenomenon is not the response of the individual sandfly larvae to lowered temperature or other external factors but is characteristic of that particular generation. In the laboratory, larvae undergoing the diapause stubbornly persist in that state in spite of efforts to bring them out of it. Overwintering larvae should be compared with those of the summer generations as to their ability to harbor the virus. The negative translarval transmission experiments of Sabin and others (p. 110) were done with sandflies reared during the early part of the sandfly season. Corresponding data for the positive experiments were provided by Whittingham and by Moshkovsky and others who, however, do not indicate the time of year when their studies were made.

Whatever the factors are which permit the virus to be carried over to the next sandfly generation, it has been demonstrated that it can happen at least part of the time. This provides the most likely explanation of how the virus is carried over from season to season.

**Control measures.**—The first really effective control measure against *Phlebotomus*, namely, residual DDT, was developed and tested only during

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<sup>10</sup> See footnote 9 (2) and (4), p. 113.

World War II. Control measures, together with protective measures, are discussed later.

## GEOGRAPHIC DISTRIBUTION

The principal areas where sandfly fever occurred in U.S. troops were the Middle East, China-Burma-India, and Mediterranean theaters. In general, the disease was limited to regions long known to be endemic, and outbreaks corresponded with the seasonal prevalence of sandflies (*Phlebotomus*). Whenever studies were made, association of the disease with sandflies was demonstrated. The incidence of sandfly fever in these three theaters is summarized in table 20.

TABLE 20.—Incidence of sandfly fever in the U.S. Army, by theater or area and year, 1942-45

[Preliminary data based on sample tabulations of individual medical records]

[Rate expressed as number per annum per 1,000 average strength]

Theater or area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States.....	10	0.0	0		0		0		10	0.00
Overseas:										
North America <sup>1</sup> .....	5	0.01	0		1	0.01	4	0.03		0
Latin America.....	35	.09	14	.14	10	.08	1	.01	10	.14
Europe.....	241	.06	0		1	0.00	75	.04	165	.08
Mediterranean <sup>2</sup> .....	11,206	7.32	11	.48	3,602	7.89	4,363	6.72	3,230	8.04
Middle East.....	4,399	33.06	424	70.13	2,968	55.95	912	19.73	95	3.42
China-Burma-India.....	2,941	6.57	145	16.58	934	23.58	1,447	8.58	415	1.80
Central and South Pacific.....		0	0		0		0			0
Southwest Pacific.....	115	.07	27	.38	0		53	.10	35	.04
Total overseas <sup>3</sup> .....	18,983	1.80	621	1.06	7,532	4.46	6,860	1.80	3,970	0.89
Total Army.....	18,993	0.75	621	0.19	7,532	1.10	6,860	0.88	3,980	0.54

<sup>1</sup> Includes Alaska and Iceland.

<sup>2</sup> Includes North Africa.

<sup>3</sup> Includes 41 cases on transports.

NOTE.—Absolute zero is indicated by zero in the units column; 0.0 indicates a rate of more than zero but less than 0.05 and 0.00 a rate of more than zero but less than 0.005.

## Middle East Theater

**Persian Gulf Command.**—The Middle East theater had a higher rate of sandfly fever than any other theater. The Persian Gulf Command had a particularly high rate, about 50 percent more than that of the theater as a whole. The great majority of cases occurred between April and October, with peaks occurring from June to August, chiefly in August.<sup>11</sup>

There was a steady decline in the entire theater from a rate of 70.13 per 1,000 troops, per annum, in 1942 to 3.42 per 1,000 in 1945. Rates in the Persian

<sup>11</sup> (1) Annual Report, Surgeon, Persian Gulf Command, U.S. Army, 1944. Inclosure No. 14, thereto. (2) Annual Report, Chief Surgeon, Headquarters, Medical Department, U.S. Army Forces in the Middle East, 1943.



Gulf Command, for example, which showed a peak of 235 per 1,000 in August 1943, reached only 74.91 in June and 72.37 in August 1944. The annual rates for 1943 and 1944 in the Persian Gulf Command were 60.2 and 29.79, respectively. The decrease was probably due both to improved protective and control measures and to the steadily increasing proportion of immune persons.

**British Army.**—Sandfly fever was also a problem to the British Army Middle East Forces, with a rate of 21.48 per 1,000 per annum in 1942.<sup>12</sup> This covered the areas of Egypt, Palestine, Syria, Cyprus, Sudan, Eritrea, Malta, and Aden. An outbreak in two hospitals in the Middle East (which the writer understands were in Palestine) was reported by Cullinan and Whittaker.<sup>13</sup> In both hospitals, about one-fourth of the doctors and nurses and nearly all the "other ranks" were attacked. On a single day in one hospital, one-quarter of the total strength of about 350 was sick. Of 1,910 patients admitted during the 3-month period, August to October 1942, nearly one-fifth contracted sandfly fever after admission. The height of the epidemic was between 27 August and 10 September. Cases were limited chiefly to certain wards surrounded by rubble, while others with "tidy surroundings" had relatively few. Sandfly infestation was heavy. A notable feature was that second attacks occurred in 15 percent of the cases from 2 to 12 weeks after the first, with occasionally three separate attacks.

On a visit to Palestine in 1944, the writer was informed that the British had been hampered by sandfly fever in 1943-44 at various airfields, particularly in maintaining schedules at air-training schools (p. 110).

**Cairo.**—Cairo provided an illustration of the classic epidemiology of the disease.<sup>14</sup> Although troops quartered in Cairo had a high sandfly fever rate during the summers of 1941, 1942, and 1943, the disease was hardly recognized among the native population. From verbal reports, members of the Commission on Neurotropic Virus Diseases, Army Epidemiological Board, gathered that the disease was thought to be one of childhood but that almost nothing was known of its prevalence among adult civilians. The difficulty of diagnosis and the ease with which the disease may be mistaken for influenza made it seem likely that many cases reported as influenza might actually have been sandfly fever. In this connection, the Commission cited the morbidity rates recorded in Egypt for 1938 and 1939 which showed the highest influenza frequency and the next to lowest mortality in the month of July.

American troops were quartered at the Metro Barracks near Heliopolis, surrounded by city buildings, vegetation, and trees. In spite of protective measures, Philip, Paul, and Sabin reported that the incidence of sandfly fever

<sup>12</sup> Report by Neurotropic Virus Commission, Board for the Investigation of Epidemic Diseases in the U.S. Army, dated 16 June 1943, subject: Preliminary Review on Papatasii (Sandfly) Fever as a Military Disease of the Middle East. I. Prevalence and Seasonal Data, obtained at Cairo, May 1943.

<sup>13</sup> Cullinan, E. R., and Whittaker, S. R. F.: Outbreak of Sandfly Fever in Two General Hospitals in the Middle East. *Brit. M.J.* 2: 543-545, 30 Oct. 1943.

<sup>14</sup> (1) Philip, C. B., Paul, J. R., and Sabin, A. B.: Dimethyl Phthalate as a Repellent in Control of Phlebotomus (Pappataci or Sandfly) Fever. *War Med.* 6: 27-33, July 1944. (2) See footnote 12.

in this unit during the fall of 1943 was approximately 25 percent of the entire command. During the same summer, British troops at three urban camps, comparable in location and vegetation to the Metro Barracks, also had considerable sandfly fever. At one camp, Helmieh, the incidence among the personnel of one hospital was especially high, more than half the officers, nurses, and other ranks having contracted the disease.<sup>15</sup> In contrast to the situation in Cairo itself was the experience of the American troops at Camp Russell B. Huckstep, which had been established in the desert about 12 miles from Cairo. There were no trees or other vegetation. Sandflies were rare, and sandfly fever was practically nonexistent.

**Vector species.**—*Phlebotomus papatasi*, one of the most widely distributed species of this genus, is practically the only one which has been associated with sandfly fever and is the only proved vector; that is, the only one with which experimental transmission to man has been effected. The species is found throughout the Middle East and was the one shown to be associated with outbreaks in Palestine and Cairo. Information was lacking about the specific association of sandflies with the disease in other areas in this theater.

### China-Burma-India Theater

In the China-Burma-India theater, sandfly fever was first reported in September 1942. After October, no further cases were reported until February 1943. The greatest incidence occurred from May to July, the hot, dry season. In 1943, several explosive outbreaks were confined to small areas. As high as 40 percent of the members of one command were attacked at one time.<sup>16</sup> The peak in each year was in July, the rates for that month in 1943, 1944, and 1945 being, respectively, 95.00, 26.75, and 4.80 (6.34 for Burma-India) per 1,000 troops.<sup>17</sup>

A noteworthy feature of sandfly fever in this theater was that its presence was demonstrated in areas not previously thought to be endemic. It had been generally stated to be limited to the northwestern part of India. However, a number of cases were reported from Calcutta and elsewhere in eastern India,<sup>18</sup> and in Burma in the Upper Chindwin section, around Rangoon, in Mandalay, and along the Salween River.<sup>19</sup> Nevertheless, U.S. troops in Assam and northern Burma were singularly free from sandfly fever, and it is questionable whether the disease occurred in these areas. A decrease in the reported rate per 1,000 per annum occurred from 1943 to 1945 in the China-Burma-India theater, as it did in the Middle East. General insect control measures, such

<sup>15</sup> Paul, J. R., Sabin, A. B., and Philip, C. B.: Interim Report of the Activities and Studies Carried Out by the Neurotropic Virus Disease Commission (Board for the Investigation of Epidemic Diseases, U.S. Army) in the Middle East and Sicily, April-October 1943, submitted 24 Sept. 1943.

<sup>16</sup> Field Medical Bulletin, Headquarters, Services of Supply, U.S. Army Forces, China-Burma-India Theater, vol. 2, No. 9, September 1943.

<sup>17</sup> Van Auken, H. A.: A History of Preventive Medicine in the U.S. Army Forces of the India-Burma Theater, 1942-45. [Official record.]

<sup>18</sup> War Department Technical Bulletin (TB MED) 174, July 1945.

<sup>19</sup> War Department Technical Bulletin (TB MED) 77, 2 Aug. 1944.

as the use of DDT, probably contributed to the lowered incidence during 1945. An additional factor was that during the summer of 1945 only a small part of the theater strength was stationed in or required to pass through areas where *P. papatasi* was present.

**Vector species.**—*Phlebotomus papatasi* is common in northwestern India but is not known to occur east of a line drawn roughly from Delhi to Madras, with the exception of an isolated record near Calcutta.<sup>20</sup> Its association with sandfly fever in northwestern India has been frequently cited in the literature. Shortt and others<sup>21</sup> transmitted the disease experimentally by the bites of *P. papatasi* fed on sandfly fever patients in Peshawar, Northwest Frontier Province. In the eastern half of India, a number of species are known to exist, and at least three species have been found in Burma.<sup>22</sup> There is no information, however, as to specific vectors in the eastern areas.

### Mediterranean Theater

The invasion of North Africa in November 1942 took place after the close of the sandfly season. No cases were reported until July 1943. A peak of admissions occurred in September when the rate was 8.02 per 1,000 troops per annum.

**Sicily.**—In the Sicily Campaign during the summer of 1943, there was a combined total of 14,492 cases diagnosed as sandfly fever, F.U.O. (fever of undetermined origin), and malaria (p. 172). The Commission on Neurotropic Virus Diseases visited Sicily in the latter part of the campaign (pp. 168–174). It was apparent that a large proportion of the undiagnosed fevers, and also of those diagnosed as malaria without positive blood films, were probably sandfly fever. Indeed, of 922 cases of the same group of fevers which were carefully observed at one hospital in Sicily, 637 were sandfly fever, representing an 87.6-percent proportion of the total cases (727) of sandfly fever (637), F.U.O. (4), and unclassified malaria (negative smear, diagnosed clinically) (86). If the same proportion of sandfly fever which was found among this group of “fevers” is applied to the “fever” cases in the campaign, and the proportion held throughout, approximately 8,500 may have been sandfly fever. Most of the American medical officers had had no previous experience with sandfly fever, but after the first few weeks they began to recognize it more readily as a distinct entity. The serious features from the military standpoint were not only the loss of the services of so many men but the fact that many were treated as malaria cases and needlessly evacuated to North Africa. The Sicilian campaign afforded a striking illustration of the serious threat which sandfly fever poses for an invading army of nonimmune men in the critical period of establishing a beachhead.

<sup>20</sup> Sinton, J. A.: Notes on Some Indian Species of Genus *Phlebotomus*; Further Records of the Geographical Distribution. Indian J.M. Research 14: 941–945, April 1927.

<sup>21</sup> See footnote 9(3), p. 113.

<sup>22</sup> See footnote 19, p. 118.



*Epidemiologic and entomologic studies, Italy, 1944*

The Army had further experience with sandfly fever on the Italian mainland in 1944. Early in August, Lt. Col. Ross L. Gauld, MC, 15th Medical General Laboratory, Naples, Italy began an epidemiologic study of the disease. The writer was on temporary duty in the Mediterranean area from the last week in July until December 1944 for the purpose of studying *Phlebotomus* in relation to sandfly fever. In carrying out these investigations, Colonel Gauld and the writer made a number of journeys to various parts of Italy south of the Arno River and to Palestine. The following discussion represents first-hand observations or information received in the course of this work, which were embodied in various reports, jointly or separately, to the surgeon of the North African theater.<sup>23</sup>

## NAPLES-CASERTA OUTBREAK

In 1944, a few cases were reported in June. In the first few days of July, shortly after the transfer of Headquarters, North African Theater of Operations, U.S. Army, from Algiers to Italy, there was a series of sharp, local outbreaks of sandfly fever in the Naples-Caserta area. These outbreaks tended to be limited to certain buildings, in which as many as one-third or even more of the occupants were affected. Frequently, entire offices were seriously crippled at a critical time. For example, enlisted men of Headquarters were billeted in the huge cavalry barracks across the street from the "Palace" at Caserta. The men in this building (and in a similar one occupied by the British) were most affected. Relatively few cases occurred among the officers billeted in the town or in the "tent city" in the forest behind the Palace. Troops quartered within a half mile of the cavalry barracks, as, for example, a Women's Army Corps detachment in the hospital area in the Palace grounds, had very few cases. In the heart of Naples, in certain schools used as barracks, personnel suffered severely for several weeks before control measures were carried out. A large number of Army and Navy personnel engaged in the planning of the invasion of southern France were quartered in the "block-house," a huge building in the form of a hollow square, located on a hilltop in Naples. The work was seriously threatened at an extremely critical period by

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<sup>23</sup>(1) Letter, Lt. Col. Ross L. Gauld, MC, Epidemiologist, Epidemiology Section, 15th Medical General Laboratory, 6744 Medical Center (OVHD), to Commanding Officer, 15th Medical General Laboratory, 15 Oct. 1944, subject: Sandfly Fever in PWCD. (Epidemiologic report appended.) (2) Letter, Maj. Marshall Hertig, SnC, 15th Medical General Laboratory, 6744 Medical Center (OVHD), to Surgeon, North African Theater of Operations, U.S. Army, 17 Aug. 1944, subject: Report of Trip to Rome, in Connection With Sandfly Fever and Sandflies. (3) Letter, Maj. Marshall Hertig, SnC, 15th Medical General Laboratory, 6744 Medical Center (OVHD), to Surgeon, North African Theater of Operations, U.S. Army, 7 Aug. 1944, subject: Report of Trip to Bari, Italy, for Conference on Sandfly Fever. (4) Letter (personal), Maj. Marshall Hertig, SnC, 15th Medical General Laboratory to Maj. O. R. McCoy, MC, Director, Tropical Disease Control Section, Office of The Surgeon General, 18 Sept. 1944. (5) Letter, Maj. Ross L. Gauld, MC, Epidemiologist, and Maj. Marshall Hertig, SnC, Entomologist, Epidemiology Section, 15th Medical General Laboratory, 6744 Medical Center (OVHD), to the Surgeon, North African Theater of Operations, U.S. Army (through the Commanding Officer, 15th Medical General Laboratory), 12 Sept. 1944, subject: Sandflies (*Phlebotomus*) and Sandfly Fever in the Fifth Army. (Appendixes A, B, and C, thereto.)

an outbreak of sandfly fever. Fortunately, most of the cases were limited to one corner of the building (an illustration of the sharp localization of outbreaks as encountered in Italy). There were certain rooms with 20 or 30 men in which nearly every man contracted the disease.

**First use of DDT.**—After the first part of August 1944, by which time control measures, including the spraying of quarters with DDT, had been put into general practice, the number of sharp outbreaks decreased. That this decrease probably was not seasonal was indicated by an epidemic in one unit quartered in an apartment building in Naples about three blocks from the Peninsular Base Section headquarters. During August, when no control measures were being taken by this unit, there were 30 cases among approximately 100 officers and enlisted men. *P. papatasi* was found in the sleeping quarters which occupied the fourth floor, showing that sandflies can be found in significant numbers some distance (at least 50 feet) above ground level, contrary to repeated statements in the literature. After spraying with DDT, the sandflies disappeared and the sandfly fever promptly ceased.

#### BARI AND “HEEL,” ROME, AND SOUTH OF ARNO RIVER

In Italy, the Naples-Caserta area was by far the most severely affected. At several installations of the Twelfth Air Force in the “heel” southeast of Bari, there were scattered cases during July 1944, which caused some concern. A survey of the Rome area in mid-August revealed relatively few cases. However, in a school building used as a barracks by the British, an outbreak occurred similar to the ones experienced by American troops in Naples, but on a much smaller scale. In the Fifth U.S. Army area, a survey made during the first week in September, in the region south of the Arno River from Florence to Cecina, showed that there had been very little sandfly fever. Very few sandflies were found near military installations, which were mostly located in open country or woodland away from towns and villages.

#### SANDFLY FEVER IN CIVILIAN POPULATION

Little could be learned from Italian sources about the epidemiology of sandfly fever in Italy. No published reports were located at the time these surveys were made, although several such reports were subsequently found.<sup>24</sup> Physicians in Naples and Rome had general or “textbook” information rather than specific knowledge about the disease in their own cities. The population of the endemic area seemed to be largely immune, and cases were limited to childhood infections or sporadic cases which may not have been recognized as a distinct clinical entity. In the Naples apartment house just mentioned where the disease occurred in a military unit, an investigation was made of civilian families occupying the same building. The survey was made early in Septem-

<sup>24</sup>(1) War Department Technical Bulletin (TB MED) 178, July 1945. (2) Peschle, B.: Osservazioni cliniche su un epidemia di febbre da papataci. *Pediatria* 44: 41–51, January 1936.

ber 1944 by Italian physicians "borrowed" for the purpose from one of the Allied agencies. They found several actual cases and obtained histories of others consistent with sandfly fever which had occurred during July and August.

The cases reported for the Mediterranean theater in 1944 (a total of 4,363 with a rate of 6.72 per 1,000 per annum) were mostly from Italy, and the total number which occurred was undoubtedly considerably greater than that reported. In the Caserta-Naples outbreak, many cases, particularly early in July, were reported as F.U.O., even though many medical officers recognized at the time that they were probably dealing with sandfly fever. The diagnosis of sandfly fever was made more freely in the latter part of the summer.

### GREECE

The experience of the Germans in the Mediterranean region was apparently comparable to that of the Allies, though there are few data available. Hallmann<sup>25</sup> reported that on the Greek mainland in the Athens district and on the islands about 20 percent of the German troops had sandfly fever in July and August 1941.

The writer, while engaged in work on *Phlebotomus* and DDT in Greece in 1948,<sup>26</sup> learned that the Germans who were quartered in Ellinikón, a suburb of Athens near the sea, were troubled with sandfly fever. This suburb consisted of substantial houses surrounded by open spaces and gardens. In 1945, the British troops quartered in the same suburb also were considerably affected by the disease. DDT had become available by that time, and its application promptly put an end to the difficulty. In 1948, with no organized spraying for at least a year or two, the writer found that *P. papatasi* were extremely abundant in some houses.

It was also learned that about one-fourth of the personnel of the United Nations Relief and Rehabilitation Administration living in the Athens area had sandfly fever in 1945. Their quarters were sprayed with DDT in 1946, and no further cases were reported among 2,000 employees. After 1946, the use of DDT had become general in all Greek, American, and British military installations, and from all available reports in 1948, sandfly fever was very rare.

### *Vector species*

In Italy in 1944, *P. papatasi* was found associated with sandfly fever outbreaks wherever entomologic investigations were made. The species was abundant and was practically the only one found in the affected buildings in Naples and Caserta. A number of buildings in which there had been few or no cases yielded no sandflies. In the Bari section, *P. papatasi* in small numbers was the only species found. While this species occurs throughout Italy and is

<sup>25</sup> Hallmann: Beitrag zum Pappatacifeber 1941 auf der Balkanhalbinsel. Deutsche Trop. Ztschr. 47: 64-68, February 1943. Abstract in Trop. Dis. Bull. 40: 694-695, September 1943.

<sup>26</sup> Hertig, M.: Phlebotomus and Residual DDT in Greece and Italy, Am. J. Trop. Med. 29: 773-809, September 1949.



often the dominant species, it is rather irregular in its distribution. For example, in an agricultural village near Naples, sandflies were moderately abundant, chiefly in stables. The principal species was *Phlebotomus perniciosus* with only a scattering of *P. papatasi*. These two species were occasionally found in small numbers in buildings or masonry ruins in Rome. In the Fifth U.S. Army area south of the Arno, where there was little sandfly fever among troops, *P. papatasi* was rare, while *P. perniciosus* and *Phlebotomus perfliewi* were fairly abundant, especially in stables. Until actual transmission experiments are undertaken with these and other species, they cannot be ruled out as vectors of sandfly fever. So far as Italy was concerned, however, Army experience confirmed the reported close association of *P. papatasi* with the disease.

### *Strains of virus and immunity*

The Commission on Neurotropic Virus Diseases, Army Epidemiological Board, obtained immunologically identical strains of sandfly fever virus from Sicily and the Middle East in 1943. A strain from Naples obtained in 1944 was found to be distinct, with no cross-immunity with the other strains (p. 167). This has some bearing on the general question of repeated attacks of sandfly fever. Reports from Italy and the Middle East, and information from British sources in regard to West Africa,<sup>27</sup> indicated that second attacks had occurred in the same season, especially following a change of station. In general, the evidence from both civilians and troops who remained in an area for successive years indicated that one attack confers a high degree of immunity.

## Pacific Areas

No authentic case of sandfly fever is known to have occurred either in Army personnel or in civilians during military operations in the Southwest Pacific, Central Pacific, or Western Pacific Areas.<sup>28</sup> Reports of some cases were made, but none was confirmed on further investigation.

**Japan.**—This was the only area in the Pacific for which intelligence reports indicated that sandfly fever had occurred previously. Reports stated that the disease was “prevalent over practically all of the southern part of the Japanese Empire.”<sup>29</sup> If sandfly fever did occur there, the occupation by U.S. forces was too late in the season to encounter it. Limited inquiry among the responsible medical profession in Tokyo failed to elicit confirmation of the presence of the disease in Japan, though occurrence of dengue and other confusing febrile conditions was admitted.

<sup>27</sup> (1) General Report, No. 1 Medical Research Station, Directorate of Biological Research, British Army Medical Services, dated September 1942 to March 1943, (d) Sandfly Fever and Pyrexias of Unknown Origin Resembling It. (2) See footnote 13, p. 117.

<sup>28</sup> This section on the Pacific areas was written by Lt. Col. (later Col.) Cornelius B. Philip, SnC, Executive Officer, Scrub Typhus Team, U.S.A. Typhus Commission, Headquarters, Office of the Chief Surgeon, U.S. Army Forces, Western Pacific.

<sup>29</sup> Army Service Forces Manual M354-13, Civil Affairs Handbook on Japan, Section 13, Public Health and Sanitation, 10 Feb. 1945, p. 91.

**Australia and the Philippines.**—In Australia and the Philippines, three and seven species of *Phlebotomus*, respectively, had been described. Only one species in each country, however, had been recorded as attacking man. The one in Australia is so limited seasonally and geographically as not to constitute a problem in disease transmission. The species in the Philippines has been reported as more common in certain areas at the proper season and was found actually biting troops in the San Jose area of Mindoro at a time when F.U.O.'s were recorded at the 13th and 165th Station Hospitals. Early in the action of the Western Visayan Task Force on the beachhead in this location, 20 cases of sandfly fever for the 4-week period ending on 23 February 1945 were reported to the Office of the Chief Surgeon by a portable surgical hospital. Most of the cases were later proved to be infectious hepatitis in the preicteric phase. Nevertheless, many cases of F.U.O. and denguelike fever, on which terminal diagnosis could not be changed, continued to be reported as sandfly fever by hospitals in this and other areas of the Philippine Islands. Thirteen iced sera of patients in the febrile stage at the 13th and 165th Station Hospitals, Mindoro, were forwarded by Army courier on 10 April 1945 for study by the Army Epidemiological Board in connection with an experimental assay of sandfly fever and dengue. Results of inoculation of two volunteers with a pool of two of these sera were negative. The occurrence of sandfly fever in the Philippine Islands remains doubtful.

**New Guinea.**—Many reports of "sandfly bites" were received from troops in beach areas, particularly at Oro Bay and Finschhafen. The only area in the mountains from which similar reports were received was Hollandia. In view of denguelike fevers and F.U.O.'s continuously reported in troops at the various bases, these reports were closely checked and were found in all instances to be due to minute biting flies related to *Culicoides* which are often called "sandflies" in the United States. The capability of these flies to transmit sandfly fever is unknown. Two undescribed species of *Phlebotomus* were found to be abundant in the forested areas over most of New Guinea during and following the rainy season. They were never taken in the act of biting, and troops on maneuvers or patrol in these places never reported bites of a nature attributable to *Phlebotomus*. It was presumed that the females, which were captured after recent feeding, had fed on reptiles or other local vertebrate fauna and not on man.

Sera from patients with fevers of short duration and doubtful diagnosis were returned from New Guinea by courier for use in volunteers in the aforementioned study. Four strains of typical dengue were recovered, but no serum produced sandfly fever.<sup>30</sup>

Although cases of sandfly fever were reported at certain bases in New Guinea, there was no presumptive evidence that the disease occurred in troops during action in New Guinea and adjacent islands in the Southwest Pacific Area.

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<sup>30</sup> Philip, C. B.: Infectivity of Dengue Serums Transported in Ordinary Ice by Air. Bull. U.S. Army M. Dept. 5(2) : 226-227, February 1946.

## CONTROL AND PROTECTIVE MEASURES

Before the war, no reliable method of controlling *Phlebotomus* was known. In the Mediterranean and the Middle East, the British for many years had practiced certain palliative measures, such as removing rubble, cementing masonry cracks, and treating soil, particularly cracked soil, around barracks with creosote or oil. Protective measures consisted chiefly of the use of fine-mesh bednets, the importance of which has long been recognized. Strong currents of air, either natural or produced mechanically, were found to be of some value. Direct killing by means of sprays was also employed. The only repellent available was citronella oil, of rather limited usefulness.

### Repellents

At the beginning of the war, insect repellents became the subject of intensive research by Government agencies and the Armed Forces, chiefly in connection with mosquitoes and malaria. New repellents were adopted by the Army in 1942 and were issued toward the end of that year. Indalone (butopyronoxyl), the first repellent issued, was superseded early in 1943 by the much more effective Rutgers 612 (2-ethyl-1,3-hexanediol), and by dimethyl phthalate. These in turn, as stocks were used up, were replaced by a 6-2-2 mixture of dimethyl phthalate, "612," and Indalone; this mixture was adopted late in 1943.

**Experimental tests.**—Studies carried out by the Commission on Neurotropic Virus Diseases, Army Epidemiological Board, in Cairo in 1943 showed dimethyl phthalate to be effective against *P. papatasi* for a period of 5 to 7 hours. In an experiment involving two groups of soldiers, cases of sandfly fever in a group which used the repellent were markedly fewer than in one which did not.

Tests of repellents "612," dimethyl phthalate, and the 6-2-2 mixture carried out in Peru in 1944<sup>31</sup> showed that all three were approximately of equal effectiveness against local species of *Phlebotomus*. They gave protection for at least 3 hours and at times for as long as 5 hours. These repellents, developed for protection against mosquitoes, proved to be even more effective against sandflies.

It was the personal experience of those conducting investigations in Peru,<sup>32</sup> Italy, and Palestine that conscientious use of any of the Army repellents provided complete protection against sandfly bites. However, it was the practically universal experience during the war that it was difficult to get troops to use repellents against either mosquitoes or sandflies except when the men were suffering pronounced annoyance from insect bites.

<sup>31</sup> Hertig, M., and Fairchild, A. G. B.: Studies on Repellents, Sprays, and Other Control Measures Against *Phlebotomus* Carried Out in the Rimac Valley, Peru, December 1943, January 1944. Monthly Progress Report No. 4, Contract No. OEMcmr-29, Suppl. No. 2, for Committee on Medical Research of the Office of Scientific Research and Development, 15 Feb. 1944.

<sup>32</sup> Hertig, M., and Fairchild, G. B.: The Control of *Phlebotomus* in Peru With DDT. *Am. J. Trop. Med.* 28: 207-230, March 1948.



## PROTECTIVE MEASURES IN VARIOUS THEATERS

Prior to the introduction of DDT in 1944, the protective measures against sandflies employed by the U.S. Army consisted of the use of (1) the sandfly net (about 30 meshes to the linear inch) which was issued instead of the mosquito bar made of ordinary netting (about 18 meshes to the inch), (2) repellents, and (3) pyrethrum sprays or the Freon-pyrethrum aerosol bomb. Removing or oiling rubbish heaps and rubble and oiling areas around tents and buildings were occasionally carried out.<sup>33</sup>

**India.**—In India in 1943 and 1944, no special protective measures against sandflies were used. Bednets were not of the fine-mesh type. Repellents and insecticides, though used as general measures against insects, were not issued in sufficient quantity until later. In 1945, DDT residual spray was commonly employed throughout the theater, both in military installations and in nearby native dwellings.

**Italy.**—In Italy, antisandfly measures were instituted within a short time after the outbreak of sandfly fever early in July 1944. They consisted chiefly of the use of repellents, sandfly nets, and the aerosol bomb, and, in some cases, spraying with DDT. In the surveys made by the writer in August 1944, it was found that there was considerable carelessness and irregularity in the use, maintenance, and method of using bednets. Also, a number of the nets were of the coarse-mesh type, which provided no protection against sandflies. Repellents were not being systematically applied by the troops. Efforts were made to correct these conditions, with some success. Very few of the U.S. personnel, including medical officers, had any real information about sandflies or even any idea of what they looked like, although in a number of instances sandflies were abundant and in plain sight on smooth white walls near beds. The demonstration to both officers and enlisted men of live sandflies and how to look for them was found to be a great aid in arousing interest and securing cooperation in carrying out protective measures.<sup>34</sup>

The results of the Freon-pyrethrum aerosol bomb were not evaluated at the time in terms of sandfly reduction. It is known, however, from studies made in Peru that thorough spraying with pyrethrum or with the aerosol bomb provides a high degree of protection for a number of hours or even an entire night.

**DDT in Italy.**—The residual spraying of quarters with DDT was practiced on an increasing scale in Italy during the summer of 1944, usually in connection with malaria control. By the first of August, it had become virtually routine to use DDT wherever outbreaks of sandfly fever appeared. The DDT, combined with other protective measures, usually caused a prompt improvement of the situation. In studies made during the latter part of the summer,

<sup>33</sup> Monthly Sanitary Report, Persian Gulf Service Command, 11 Aug. 1943.

<sup>34</sup> For the instruction of entomologists, parasitologists, and medical officers, several Italian species of *Phlebotomus* were reared at the 15th Medical General Laboratory. While the technique is not widely known by American entomologists and requires some skill and experience, it has become more or less standard and is described in the literature of experimental studies on the sandflyborne diseases.

it was found that wherever DDT spraying had been adequately carried out, sandfly fever had ceased, and no more sandflies were to be found. The spraying was not always done well. For example, the cavalry barracks at Caserta were sprayed within 2 weeks after the outbreak began, with some improvement in the sandfly fever situation. However, only hand sprayers were available for treating this large structure which had very high ceilings. The result was that only about one-quarter of the necessary quantity of DDT was applied, and the coverage was very uneven. Sandflies continued to be moderately abundant in the building. The spraying was done again, more thoroughly, and the sandflies disappeared.

Controlled experiments were not possible in military installations where all available protective measures were used simultaneously. However, observations at various places in Italy, where DDT spraying was done either in connection with sandfly fever or for other purposes, together with the experimental work to be discussed, warrant the conclusion that DDT residual spray was the most effective single method of sandfly control.

### Experimental Studies With DDT

Preliminary experiments with DDT residual spray in Peru in 1944 gave promising results. The flight habits of all known species of *Phlebotomus* render them extremely vulnerable to the residual action of DDT. They proceed normally by means of very short flights with relatively long pauses, so that in the process of entering a building they spend considerable time on both the outer and inner walls before attempting to feed (fig. 5).

**Toxicity of DDT for *Phlebotomus*.**—In Italy, it was found that contact for 2 or 3 minutes with residual DDT caused agitation of sandflies and that in the case of two species a lethal dose was secured within 6 to 15 minutes; *P. papatasi*, however, required from 15 to 30 minutes.

**Experiments, Naples.**—Spraying the outer walls of stone stables in a village near Naples reduced to stragglers the sandflies which could be found inside, while normal numbers were found in untreated buildings. *P. perniciosus* was the principal species in this area. The effect lasted throughout the 4 to 5 weeks of observation.

**Experiments, Palestine.**—In Palestine, controlled experiments were carried out near the Dead Sea in October and November 1944<sup>35</sup> where *P. papatasi* is extremely abundant (fig. 6). It was found that spraying the inner walls and ceilings of buildings provided complete control, with no bites reported, while spraying the outer walls or merely the doors and windows, together with a foot or two of the wall surrounding such openings, reduced sandflies by about 75 percent and gave comparative freedom from bites. An experiment with sprayed tents, although interrupted, indicated that the results would be comparable. It was recommended that rooms be sprayed inside, together with open-

<sup>35</sup> Hertig, M., and Fisher, R. A.: Control of Sandflies With DDT. Bull. U.S. Army M. Dept. 88(3): 97-101, May 1945.



FIGURE 5.—Spraying Arab hut with 5 percent DDT in kerosene, Algeria. Residual DDT applied to inner walls, together with outside of doors and other openings, gives effective sandfly control.

ings and a little of the surrounding outer wall (fig. 5). In northern Palestine, a stone wall from which numerous sandflies (*Phlebotomus major*) emerged at night yielded no sandflies after spraying, while normal numbers were caught on an unsprayed wall nearby. This experiment indicated that DDT could deny to sandflies their customary outdoor resting and breeding places.

#### *Area control with DDT*

**Peru.**—Experimental studies carried out in Peru in 1945 indicated that area control (that is, control of sandflies outdoors as well as indoors) could be obtained within a radius of 100 to 200 meters by spraying with DDT those outdoor structures, especially loose-laid stone walls, which harbor sandflies or serve as breeding places, or on which sandflies alight in flying toward a blood meal (fig. 7). Such surfaces, if properly selected, would not only eliminate the principal resting and breeding places but would form a series of lethal barriers to the movement of sandflies within the area (figs. 4, 6, and 7).

In one experiment, the combined spraying of a house and surrounding walls virtually eliminated sandflies on the premises, an effect which persisted for over a year and a half, while in houses 75 to 200 meters distant sandflies





FIGURE 6.—Two views of house being sprayed with 5 percent DDT in kerosene. (Experimental studies on control of *Phlebotomus* with DDT near Dead Sea, Palestine.)

were normally abundant. As part of the Peruvian work in 1945, practical control projects were started in two large construction camps and then carried on by the engineers in charge. Residual DDT was applied to the interiors of buildings and also to some outdoor walls. The sandflyborne diseases were bartonellosis and some cutaneous leishmaniasis. Both ceased to be problems. On visits to Peru by the writer in 1947 and 1950, it was learned that control of both sandflies and disease continued to be complete. One project had terminated in 1946, but another had been started in 1947. Two projects were in operation in 1950. There had been no bartonellosis or leishmaniasis among the 3,000 workmen exposed.

**Greece, Crete, Sardinia, and Italy.**—The writer has had other opportunities of confirming the effectiveness of residual DDT in controlling *Phlebotomus*. Observations in Greece, both on the mainland and in Crete in 1948 (p. 122), showed that the application of residual DDT on the inner walls and ceilings of houses (primarily for malaria control) had reduced *Phlebotomus* within the sprayed villages almost completely, while they were abundant in some unsprayed places. Most of the villages had been sprayed during 3 consecutive years. It was the universal testimony that sandflies had been abundant but had “disappeared” with the first spraying. The dominant sandfly in unsprayed areas was *P. papatasi*. During the same summer, it was found both in Sardinia and in the Italian Province of Abruzzi that the application of DDT had had a similar devastating effect on *Phlebotomus*.



FIGURE 7.—Loose-laid stone wall. Typical breeding place and daytime shelter of *Phlebotomus*. (Experimental studies, DDT-sandfly control, Peru.)

### *Sandfly control: General recommendations*

From these various experiments and observations with several species of *Phlebotomus* in both tropical and temperate regions, the writer considers it established that sandflies are extremely vulnerable to residual DDT and that a single annual application, preferably before the sandfly season, will give virtually complete control within dwellings or other buildings and, in the case of compact communities, within the area as well.

For military operations within a sandfly area, the writer would recommend that in addition to the conscientious use of the protective measures already discussed—repellents, sandfly net, aerosol bomb—the interiors of all structures or tentage, but especially of living quarters and animal shelters, be treated with residual DDT before the sandfly season, or as soon as possible if the season has already begun. The danger from sandfly fever would be especially great in buildings recently vacated or still occupied by local people, since such places would have the greatest concentration of both sandflies and sources of infection.

**Jungle or forest.**—In jungles or forests, the data are rather scanty in regard to sandfly control. However, with the exception of leishmaniasis in South and Central America, there are not known to be any serious sandfly problems in such habitats. The spraying of jungles from the air, which was extensively investigated and practiced for mosquito control during World



War II, would also doubtless destroy many adult sandflies along with the mosquitoes. This was indicated by incidental observations made by the writer on sandflies during airspray experiments carried out by the U.S. Army in Panama in 1945, but the data are not conclusive since the experimental areas to begin with had relatively few sandflies.

In the event of military operations in a forest area where sandflies were disease transmitters or pests, residual DDT on tentage or structures could be expected to give indoor protection. In addition, the writer considers it probable that considerable reduction of sandflies in the immediate area could be achieved by spraying exposed rocky surfaces and the buttresses and trunks of larger trees, with particular attention to hollow trees and to places where animals were picketed or corralled. This statement is based on the writer's observation on the habits of sandflies in forests both in Panama and in Paraguay. They commonly alight on larger objects in their path, which could be rendered lethal by DDT.

**Airspray.**—The effect of airspray in village or urban areas may merit investigation. A suburb of Athens was sprayed from the air during the summer of 1946. There was consistent local testimony that sandflies had been abundant but ceased to give annoyance. Since a method of this type might have military applications, it would be desirable to determine experimentally the limits of its usefulness.

## SUMMARY

Of the sandflyborne diseases, only sandfly fever was an important military problem during World War II. A general account of the epidemiology and military history of the disease is given. Over 18,000 cases were reported in U.S. troops from the Middle East, Asiatic, and Mediterranean theaters (table 20). Undoubtedly, a great many additional cases were reported as F.U.O.'s, and it is probable that the total of sandfly fever cases approached 24,000. Areas with particularly high rates were Sicily (during the invasion in 1943), and the Persian Gulf Command.

The greatest incidence among troops in actual combat was during the Sicily Campaign in the summer of 1943. Military operations were also hampered by sandfly fever in Italy in 1944.

Sandfly fever occurred only in known endemic areas, with the exception of the eastern part of India and parts of Burma where it had not previously been recognized. Association with *P. papatasi*, known to be a vector, was demonstrated in Italy and the Middle East. Species of *Phlebotomus* were present in all areas where the disease occurred.

Special studies on the etiology and transmission of sandfly fever were carried out in the Mediterranean and Middle East theaters in 1943. Two immunologically distinct strains were isolated. Epidemiologic and entomologic studies were made in Italy and Palestine during 1944.

In all theaters, the standard protective measures against biting insects, including mosquitoes and sandflies, were available. These consisted chiefly



of repellents, sandfly nets, and the Freon pyrethrum aerosol dispensers. These materials, when properly used, were proved to be effective, but their application was sometimes irregular. Control studies made in Italy, Palestine, Peru, and Greece showed that the DDT residual spray was extremely effective against sandflies. The method of applying residual DDT, which has become standard in malaria control, namely, spraying the inner walls and ceilings of dwellings and animal shelters, also gives virtually complete protection against sandflies indoors and, in the case of compact communities, outdoors as well as within the treated area.

## Part II. Experimental Studies

*Albert B. Sabin, M.D.*

### HISTORICAL NOTE

All that was known with certainty in 1940 concerning the virus of sandfly fever was that it was a filterable agent present in the blood of patients 1 to 2 days before and for 1 day after onset of the fever, and that *P. papatasi* was capable of transmitting the infection from man to man. Since the clinical manifestations of sandfly fever are not in themselves sufficiently characteristic to permit identification of an unknown, filterable agent, it was clear to the critical investigator that primary identification of the virus of sandfly fever was a difficult matter which could not be regarded as complete without the demonstration of its transmissibility by *P. papatasi*. Since this type of critical identification was apparently too difficult for most investigators, the literature contained a good many incomplete observations and conclusions based on inadequate data which at best left the subject in a somewhat confused state.

The work reported by Shortt and his associates<sup>36</sup> in India between 1934 and 1939 was particularly intriguing, although inconclusive. These investigators reported that human infectious serum (presumably containing the sandfly fever virus) produced a febrile illness in *Macaca rhesus* monkeys. Although the blood of such monkeys upon inoculation in human volunteers produced, after an incubation period of 5 to 7 days, only vague symptoms of headache and generalized malaise without distinct fever (which might have been mild serum sickness), and although no studies on the leukocytes were carried out nor passage to other volunteers attempted, it was, nevertheless, concluded that sandfly fever "appears" to have been transmitted to monkeys.

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<sup>36</sup> (1) Shortt, H. E., Poole, L. T., and Stephens, E. D.: Sandfly Fever on the Indian Frontier; A Preliminary Note on Some Laboratory Investigations. *J. Roy. Army M. Corps* 63: 361, December 1934; 64: 17, January 1935. (2) Shortt, H. E., Rao, R. S., and Swaminath, C. S.: Cultivation of the Viruses of Sandfly Fever and Dengue Fever on the Chorio-allantoic Membrane of the Chick-Embryo. *Indian J.M. Research* 23: 865-870, April 1936. (3) Shortt, H. E., Pandit, C. G., and Rao, R. S.: The Virus of Sandfly Fever in Culture and Certain of Its Properties. *Indian J.M. Research* 26: 229-239, July 1938.

Shortt and various associates also reported that infectious human serum (again presumably containing the sandfly fever virus) produced lesions on the chorio-allantoic membrane of embryonated eggs, which could be transmitted in series with filtered extracts of these membranes and be prevented from developing by the serum of patients convalescent from sandfly fever. They concluded from these data that "the virus of sandfly fever has been cultivated by the chorio-allantoic membrane technique and in tissue culture and the cultures carried through numerous passages." Then, on the assumption that the production of lesions on the chorio-allantoic membrane could be used as an indicator of the presence of virus, these investigators reported on various properties of this virus. Thus, the virus was said to have a size of 160 m $\mu$ .<sup>37</sup>

In a communication presented at the Third International Congress of Microbiology in 1939, Shortt and his coworkers<sup>38</sup> summarized their studies on the sandfly fever virus as follows:

This virus has been maintained in culture on the chorio-allantoic membrane of chick embryos and in tissue culture for 61 and 41 passages, respectively.

*The cultured virus has been shown to possess no pathogenic properties for man and laboratory animals, whatever the route of inoculation.*

The virus has been demonstrated in the bloodstream of monkeys inoculated subcutaneously up to a maximum of 19 days. In human cases of the disease occurring naturally, the virus is usually demonstrable in the bloodstream for 7 days, and in one case was demonstrable for 28 days.

In the case of inoculated monkeys, neutralizing antibodies have been found present up to at least 69 days. Attempts at the prophylactic inoculation of human beings with a vaccine containing live virus have been made. Two doses of vaccine, with a week's interval between doses, were given. In the inoculated persons, the presence of virus circulating in the peripheral blood was demonstrated 5 days after the second dose of vaccine. Thirty-five days after the second dose of vaccine the sera of some of the vaccinated persons showed the presence of neutralizing antibodies, while those of others similarly vaccinated failed to do so. Infection of the vaccinated persons and controls with infective serum from sandfly fever cases gave inconclusive results.

Thus, although the cultured virus was not pathogenic for man and the infection experiments in persons vaccinated with this cultured material gave inconclusive results, these investigators did not entertain the conclusion that they might not be dealing with the virus of sandfly fever. Furthermore, although in experiments on human volunteers the virus of sandfly fever had not been found beyond 24 hours after onset of the fever, the chorio-allantoic membrane technique seemed to reveal the presence of a lesion-producing agent (virus?) for as long as 7 days and, in one instance, for 28 days.

While the experiments of Shortt and his coworkers with chick embryos were thus inconclusive, they were, nevertheless, followed by reports of Russian workers in 1940 and 1941 which, however, did not become available to us until

<sup>37</sup> The figure of 160 m $\mu$  should actually have been given as 190 to 285 m $\mu$ , since the membrane with an average pore diameter of 480 m $\mu$  just permitted the "activity" to pass, while the 380 m $\mu$ -membrane held it back. Using Elford's generally accepted formula, the particle size should have been taken as  $\frac{1}{2}$  to  $\frac{3}{4}$  of 380 m $\mu$ .

<sup>38</sup> Shortt, H. E., Pandit, C. G., and Anderson, W. M. E.: Studies on Sandfly Fever. Abstracts of Communications, Third International Congress for Microbiology, 1939, p. 133.

they were abstracted in the *Tropical Diseases Bulletin* in April 1943. In the 1940 report, Demina and Levitanskaja<sup>39</sup> stated not only that the sandfly fever virus (serum of patients with the disease) produced lesions in the chorio-allantoic membrane, which could be prevented by immune serum, but also that the whole membrane and whole embryos produced "typical phlebotomus fever" in eight human volunteers. It was added, however, that "injection into seven volunteers of [suspensions of] pieces of chorio-allantoic membrane taken near the site of inoculation (from primary and subcultures) failed to produce infection or immunity." In the 1941 report, Demina<sup>40</sup> stated that sandfly fever virus inoculated directly into the yolk sac of chick embryos produced cultures in which both the chorio-allantoic membrane and embryo were virulent, as demonstrated by successful infection of mental patients. The abstract further went on to say:

\* \* \* Of the two strains maintained by her, one was virulent after 30 subcultures, the other after 26, though in both the virulence was continuously manifested only till the tenth subculture. Later passages behaved in an irregular manner, some losing not only their virulence but also their antigenic properties.

Aside from these rather conflicting reports on the behavior of the sandfly fever virus in chick embryos, the available data indicated that no clinically apparent disease was produced in guinea pigs, rabbits, or dogs as a result of extraneural injection of human serum containing the virus. There was no record that the method of intracerebral inoculation of rodents had been explored.

As regards the natural history of the virus, nothing was known of its possible presence in hosts other than man and *P. papatasi*. It was assumed that the virus persisted in nature as a result of transovarian passage from one generation of infected *Phlebotomi* to another—an assumption which received considerable support from the rather detailed experiments on human volunteers reported in 1937 by the Russian investigators, Moshkovsky and his associates.<sup>41</sup>

## OBJECTIVES OF RESEARCH

The high incidence of sandfly fever among British troops stationed in Palestine and the Middle East<sup>42</sup> since 1939 and its appearance among American troops in the Middle East and the Persian Gulf Commands,<sup>43</sup> as well as in the Asiatic theaters in 1942 (p. 118), led the Commission on Neurotropic

<sup>39</sup> Demina, N. A., and Levitanskaja, P. B.: Studies on Pappataci Fever. X. Attempts to Cultivate the Virus on the Chorio-allantois of Chick Embryo. *Med. Parasitol. (Moscow)* 9: 272-284, 1940. Abstract in *Trop. Dis. Bull.* 40: 305, April 1943.

<sup>40</sup> Demina, N. A.: Studies on Pappataci Fever. XI. Further Investigations on the Pappataci Virus in Culture. *Med. Parasitol. (Moscow)* 10: 271-283, 1941. Abstract in *Trop. Dis. Bull.* 40: 305, April 1943.

<sup>41</sup> Moshkovsky, S. D., Demina, N. A., and others: Studies on Pappataci Fever. VIII. On the Presence of the Virus in *Phlebotomi* Born From Eggs Laid by Infected Females. *Med. Parasitol. (Moscow)* 8: 922, 1937.

<sup>42</sup> (1) Walker, A. S., and Dods, L.: Clinical Impressions of an Epidemic of Sandfly Fever in Palestine During 1940. *M.J. Australia* 1: 345-349, March 1941. (2) See footnote 13, p. 117.

<sup>43</sup> See footnote 15, p. 118.



Virus Diseases, Army Epidemiological Board, to undertake experimental studies on this disease. The first group to concern itself with this work consisted of Dr. John R. Paul, Director of the Commission; Maj. (later Col.) Cornelius B. Philip, SnC, an entomologist; and this author, a virologist. This group of workers made a preliminary survey of the disease in the Middle East and Palestine and set up an experimental ward and laboratory as part of the 38th General Hospital at Camp Russell B. Huckstep in the desert approximately 8 miles outside of Cairo. One building was especially altered for this purpose and screened with special care against sandflies. It was ready for use on 20 May 1943 and was maintained as an active laboratory until 15 December 1943. The objectives of research on this disease were as follows:

1. As an immediate step, to determine whether any of the available mosquito repellents might be effective in protecting against the bites of *P. papatasi*, a procedure which might then be used in an attempt to protect against this disease.
2. To recover one or more strains of the virus of sandfly fever by reproduction of the disease in human volunteers and to make positive identification by transmission through *P. papatasi* raised in the laboratory from ova of flies previously proved to be noninfective.
3. To attempt to infect a large variety of lower animals and to cultivate the virus in embryonated eggs, simultaneously with the work on infection of human volunteers.
4. To develop an adequate source of the virus from lower animals, embryonated eggs, insects, or human beings, which might be used for the elaboration of a specific diagnostic test as well as for studies on artificial immunization against the disease.
5. To investigate the possibility of transmission by vectors other than *P. papatasi*, especially parasitic arthropods indigenous to epidemic zones and mosquitoes prevalent in the United States.

## EFFECTIVENESS OF REPELLENTS UNDER NATURAL CONDITIONS

In May 1943, nothing was as yet known regarding the effectiveness of DDT against *P. papatasi*. It was also clear at that time that no matter how successful the experimental studies on sandfly fever during the coming summer might prove to be, they would have nothing to offer in the way of specific biologic control during the 1943 season. An immediate investigation of the possible value of insect repellents then available to the Army in large quantities was, therefore, indicated as a measure which might be of practical value in the control of the disease in the forthcoming months. This study was carried out with the help of Prof. S. Adler and Mr. S. Arkin, of the Hebrew University in Jerusalem. Lt. Col. C. H. S. Little, British Deputy Director of Medical Services in Palestine, not only lent his cooperation but also served as a volunteer in the studies. Two repellents, greaseless and practically odorless after application, were investigated: (1) A British preparation consisting

of a vanishing cream containing pyrethrum, and (2) an American fluid preparation (called Skat commercially) containing dimethyl phthalate. Professor Adler pointed out, and it was later confirmed by observation, that during a period of study as short as 15 minutes the largest number of bites and feeds might be expected from *Phlebotomi* contained in a closed test tube, a lesser number from flies in an open gauze-covered tube, and least of all from flies in a fairly large muslin-covered wire cage. Areas of skin (about 1.5 cm. in diameter; that is, the internal diameter of the test tube) on the flexor surface of the forearms either treated with repellent or untreated were to be exposed to approximately 20 unfed *Phlebotomi*. While this method of testing did not reproduce natural conditions, it, nevertheless, provided a technique by which the effectiveness of different repellents could be estimated and compared. To supplement these tests, the same repellents were also studied under natural conditions in sleeping rooms occupied simultaneously by treated and untreated individuals. The large numbers of *Phlebotomus* flies required for these tests could be obtained on short notice at that time of the year only at the Dead Sea post where quarters and facilities for this work were obtained through the courtesy of the Palestine Potash Company. Mr. Belferman, the malaria control officer of the company, not only made all the arrangements for the working and sleeping rooms but also helped find and catch the *Phlebotomi* which were needed for the experiments. Seven American volunteers of the Levant Service Command, attached to the 24th Station Hospital in Tel-Litwinsky, Palestine, participated in this study.

The closed-tube tests summarized in table 21 indicated that both the British and American preparations possessed repellent properties but that the effects produced by them under the special experimental conditions were somewhat different:

1. The protection afforded by dimethyl phthalate, while it lasted, was almost complete against both biting and feeding. With the British cream, however, the bites were greatly reduced in number but not entirely prevented although, with few exceptions, it so affected the treated skin that the flies failed to feed on it for a longer period than in the case of the dimethyl phthalate.

2. With dimethyl phthalate, the period of protection ended, that is, the flies bit and fed again as on the control areas, at 6¼, 7, and 8 hours, respectively, in the three subjects. With the British cream, a definite endpoint was not established because the protection was only partial against biting throughout the period of the test, but still practically complete at the end of 9 hours as regards the failure of the flies to engorge on the treated skin.

The open-tube tests were unsatisfactory except in two volunteers who were treated with dimethyl phthalate. The results again indicated that this preparation protects for 6 to 7 hours but not for 8 hours under the conditions of these tests. The impression gained from the control tests under natural conditions in sleeping quarters was that both the dimethyl phthalate and the British cream, when properly applied to all the exposed skin surfaces, may

TABLE 21.—*Repellent tests against P. papatasii, closed-tube method*

Repellent tested	Hours after application	Effect of applying approximately 20 female flies first to treated and then to untreated site <sup>1</sup>											
		Subject A				Subject B				Subject C			
		Treated		Untreated		Treated		Untreated		Treated		Untreated	
		Bites	Feeds	Bites	Feeds	Bites	Feeds	Bites	Feeds	Bites	Feeds	Bites	Feeds
Dimethyl phthalate.....	3	0	0	<i>20</i>	<i>10</i>	0	0	<i>21</i>	<i>15</i>	2	2	0	6
	4	0	0	0	0	0	0	2	0	1	1	0	0
	6¼	1	1	4	2	0	0	4	2	10	6	6	5
	7	0	0	20	10	21	7	2	0	13	7		
	8	9	8	22	5	5	1	4	2				
British pyrethrum cream..		Subject D				Subject E				Subject F			
	3	1	0	<i>27</i>	<i>10</i>			<i>11</i>	<i>4</i>			<i>21</i>	<i>10</i>
	4	3	0	2	1	5	1	0	0	1	0	4	4
	6¼	3	0	6	0	2	0	0	0	3	0	1	1
	7	4	0	1	1	4	2	2	0	2	0	5	1
	8	6	2	4	2	4	0	5	2	5	0	0	0
	9	3	0	5	3	2	0	7	3	5	0	2	2

<sup>1</sup> Flexor surface of left forearm treated with repellent; right forearm untreated; different batches of 20 flies were used for each test.

<sup>2</sup> The failure of the flies previously exposed to the treated side to bite or feed on the untreated side shows the extent to which the flies were "knocked out" by the repellent.

NOTE.—The italic figures represent the behavior of the flies on the untreated skin and are the control for evaluating the effectiveness of the repellents tested.

give adequate protection against the bites of *P. papatasii* during the usual 8-hour period of sleep (table 22).

None of the exposed American volunteers developed sandfly fever, suggesting that the *Phlebotomi* which were used either had a very low infection rate or were uninfected—a factor of importance since the progeny of these flies were subsequently used for the experimental transmission tests in the desert laboratory.

As a result of these studies <sup>44</sup> and in the absence of any specific immunologic methods of control, it was believed that for 1943 repellents might probably be used with profit in attempts to reduce noneffectiveness due to disease and loss of sleep resulting from the bites of *P. papatasii*. The studies indicated that in routine practice two applications of the repellent would be required, one at sunset and one before retiring. It was estimated that the total amount of liquid repellent required per man per day would be about 10 cc.

<sup>44</sup> (1) Letter, Maj. Albert B. Sabin, MC, Virus Commission, Headquarters, U.S. Army Forces in the Middle East, to Col. S. Bayne-Jones, MC, Division of Preventive Medicine Service, Office of The Surgeon General, 14 June 1943. Report enclosed thereto, subject: Preliminary Observations on the Effectiveness of Certain Repellents Against *Phlebotomus papatasii*. (2) See footnote 7, p. 110.



TABLE 22.—*Effect of repellents under natural conditions in sleeping quarters at night*

Room	Subject	14 May 1943		15 May 1943	
		Treatment	Result	Treatment	Result
1	S-----	Untreated----	Unable to sleep because of innumerable bites all through the night until 6 a.m. when subject arose.	Untreated for first 10 minutes. Dimethyl phthalate. Exposed untreated chest at 6 a.m.	25 bites.  Slept through night; no bites. 2 bites within 2 minutes.
	L-----	British cream applied 12:30.	Slept through night; 1 bite on arm, 7 a.m., 1 bite on ankle, 8 a.m.	Untreated for first 10 minutes.	25 bites.
2	Sa-----	Untreated----	Unable to sleep because of innumerable bites.	Untreated-----	Unable to sleep because of innumerable bites.
	Se-----	British cream applied 10:45 p.m.	No bites felt; slept right through night.	British cream----	No bites; slept right through night.
	P-----	Dimethyl phthalate, 11 p.m.	No bites; slept right through night.	Dimethyl phthalate.	Do.
	D-----	Untreated----	Felt no bites; slept well. <sup>1</sup>	Untreated-----	Bitten many times.
3	A-----	-----do-----	-----do. <sup>1</sup> -----	-----do-----	Bitten many times; unable to sleep.
	Do-----	British cream----	-----do. <sup>1</sup> -----	British cream----	No bites felt; slept right through night.
	Dr-----	Dimethyl phthalate.	-----do. <sup>1</sup> -----	Dimethyl phthalate.	Do.

<sup>1</sup> It was a cool night and subjects completely covered themselves with blankets.

NOTE.—Approximately 150 unfed female *P. papatasi* liberated in each room on the night of 14 May. On the night of 15 May, approximately 140 were liberated in room 1, 125 in room 2, and 200-250 in room 3.

The effectiveness of dimethyl phthalate for the control of sandfly fever under natural conditions was tested during a small outbreak among Americans quartered in an inhabited area of Cairo, Egypt, during September and October 1943. The results, published in detail, by Philip, Paul, and Sabin <sup>45</sup> were as follows:

The men in a given barracks were divided into two groups. The repellent was issued to one group [82 men to begin with] and an inert control solution to the other [88 men to

<sup>45</sup> See footnote 14(1), p. 117.

begin with]. Directions for the application of these solutions when the men retired at night were the same for each group. Of the men receiving the repellent, 42 percent reported relief from bites; of those receiving the control solution, 12 percent reported relief. Of the men receiving the repellent, 2 acquired sandfly fever during the 5-week experimental period; and of those receiving the control solutions and no solution, 12 acquired sandfly fever. Both men who "used" the repellent and acquired sandfly fever acknowledged that they had not followed directions and had failed to apply it for several consecutive nights prior to acquisition of the disease. \* \* \* Dimethyl phthalate as an insect repellent is recommended as a method for the control of sandfly fever. It has been tested during an epidemic and shown to be of apparent value.

## STUDIES ON AMERICAN VOLUNTEERS IN EGYPT, 1943

**Recovery of agent.**—The source of sandfly fever virus was the blood of patients in the first 24 hours of the disease. The patients came from among British troops who had contracted the disease in the vicinity of Cairo and from among U.S. troops stationed at Deversoir Field on the Suez Canal. Approximately 50 cc. of blood was obtained from each patient; the serum was separated and stored in the frozen state at the low temperature produced by solid CO<sub>2</sub>. The following points were established in each case before any serum was included in the pool that was to be inoculated into the human volunteers:

1. The subsequent clinical source of the disease had to be compatible with that of sandfly fever.

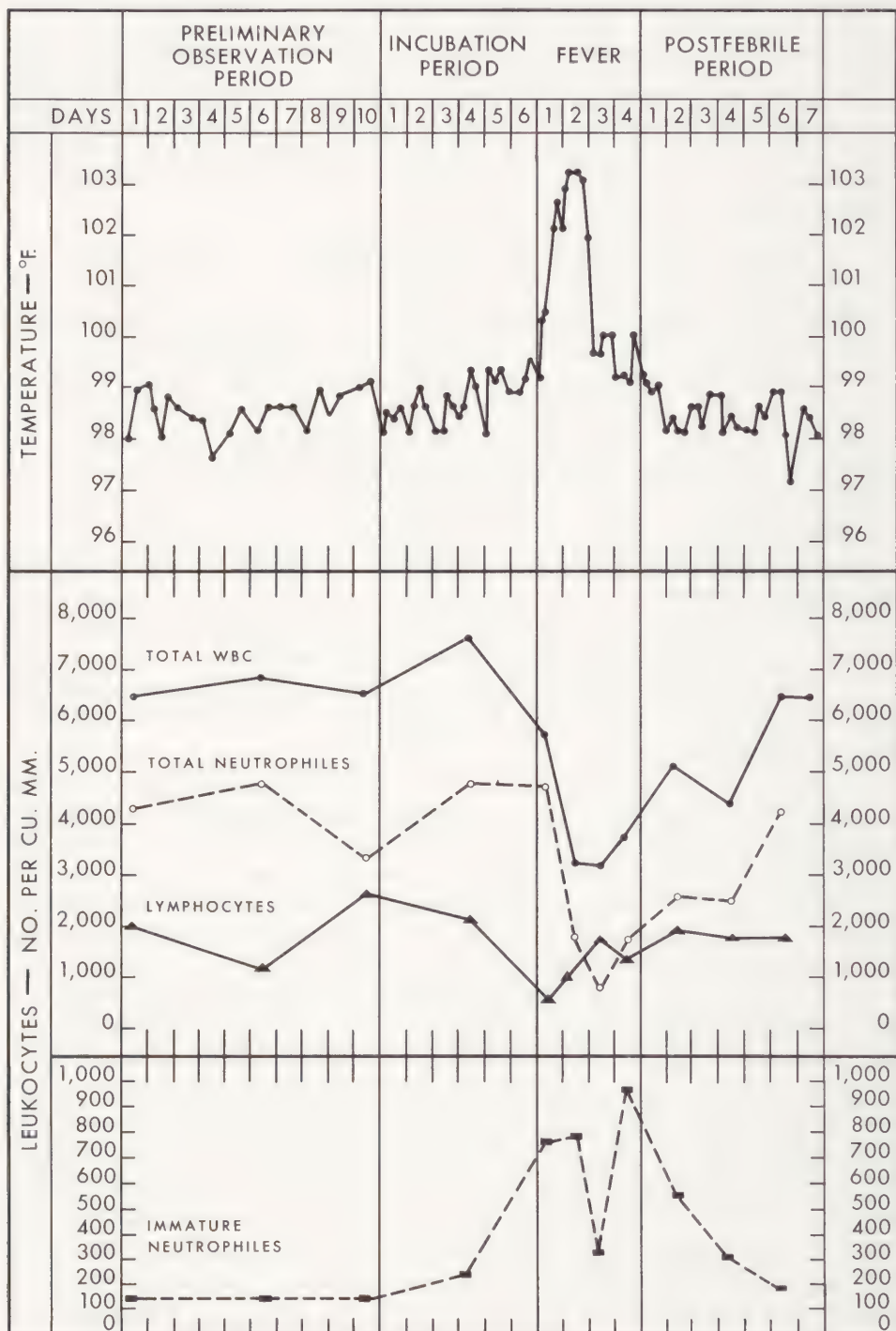
2. The presence of *P. papatasi* in the area from which the patient came had to be demonstrated by a member of the Virus Commission.

3. The patient's past history should have had nothing to contraindicate the use of his serum in other human beings—syphilis and jaundice having been especially ruled out.

4. A negative Kahn test and bacteriologic sterility had to be established.

When a sufficient amount of serum satisfying these criteria had been accumulated, a pool derived from 11 patients was prepared, and on a selected day the pooled serum was inoculated into human volunteers, monkeys, hamsters, white mice, gray mice, desert rats, rabbits, and guinea pigs. The same pooled serum was also inoculated by different routes into embryonated eggs onto the chorio-allantoic membrane, into the allantoic sac, or into the yolk sac.

The human volunteers were chosen from among U.S. troops without a previous history of sandfly fever who had arrived from the United States after the last sandfly season. They were quarantined in special, air-conditioned, sandfly-proofed rooms for a period of 10 days, the maximum known incubation period of the disease. At the end of this period of quarantine, during which baseline observations were made on temperature, pulse, and leukocyte count, each of the first four volunteers was inoculated with 1 cc. of the pool of acute sandfly fever serum—0.1 cc. intracutaneously and 0.9 cc. subcutaneously. After an incubation period of 4 to 6 days, three of the four volunteers developed the typical symptoms and fever of the natural disease (chart 3). During the course of subsequent experiments with insects, five additional volunteers were

CHART 3.—*Experimental sandfly fever in American volunteers in Egypt*



each inoculated with 0.3 cc. of the same pool of acute sandfly fever serum, and all developed the typical experimental disease after the usual incubation periods. As each volunteer developed this fever, 50 to 75 cc. of blood was obtained, and the frozen serum was saved as a supply of potentially infective virus. During the course of certain other experiments, two human volunteers were inoculated with a pool of serum from the first group of volunteers and both developed typical experimental sandfly fever after the usual incubation period. Thus, it was possible to demonstrate not only that an infective agent was obtained from the serum of patients with the naturally occurring disease but also that the bacteria-free agent was capable of transmission in series. While the circumstantial epidemiologic evidence taken together with the clinical manifestations of the experimental disease strongly suggested that the agent recovered was the virus of sandfly fever, it was, nevertheless, still necessary to satisfy another criterion; namely, that of transmission by *P. papatasi*.

**Hepatitis virus in pool of serum.**—It should be noted here that despite all the care that was taken in the selection of the original group of patients with the naturally occurring disease, the original pool of serum that was used to inoculate the first human volunteers contained, in addition to the infectious agent of sandfly fever, another agent capable of producing hepatitis with jaundice. Of the 10 human volunteers who were inoculated with this pool for the transmission of sandfly fever, 4 also developed hepatitis with jaundice 72 to 94 days after the first inoculation. The same pool of serum was subsequently injected parenterally in human volunteers in the United States and three of the five developed hepatitis with jaundice. A further complication occurred when the serum of one of these volunteers in Egypt, obtained 34 days after inoculation with the original pool and 60 days prior to his development of hepatitis with jaundice, was used after heating at 56° C. for a half hour as control skin-test material in eight of the personnel associated with the hospital and laboratory of the Commission. Three of these eight individuals developed hepatitis with jaundice after incubation periods of 94 to 132 days. The details of this intercurrent hepatitis experience were reported by Paul, Havens, Sabin, and Philip.<sup>46</sup>

**Experimental transmission of sandfly fever agent by *P. papatasi*.**—The *P. papatasi* used for these tests were reared in the Commission laboratory from ova derived from the stock collected in May 1943, in the Dead Sea area during the experiments on insect repellents. Because of the restricted residence of the local population and because the parent flies failed to produce the disease in eight American volunteers, who were bitten by large numbers of them, the stock of sandflies was regarded as uninfected and, therefore, especially suited for the transmission experiments. The other bloodsucking insects used in the first test consisted of fleas (*Pulex irritans*) collected from native clothing in an Egyptian village, and *Culex pipiens* mosquitoes collected at Deversoir

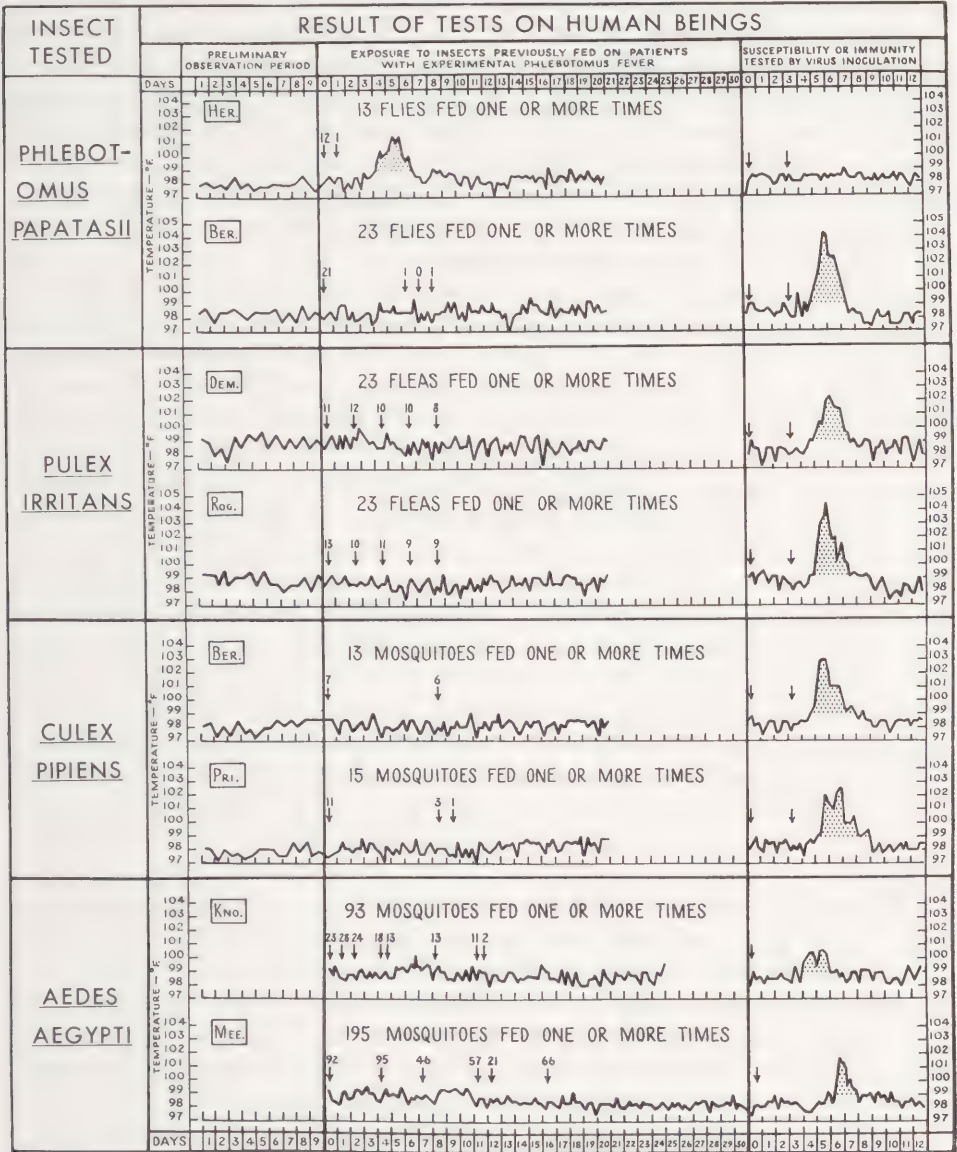
<sup>46</sup> Paul, J. R., Havens, W. P., Jr., Sabin, A. B., and Philip, C. B.: Transmission Experiments in Serum Jaundice and Infectious Hepatitis. J.A.M.A. 128: 911–915, July 1945.

Field during an outbreak of sandfly fever among American troops. These three species of bloodsucking insects were fed on three of the first group of human volunteers during the first 24 hours of the experimental disease. After extrinsic incubation periods which varied from 8 to 18 days, the survivors were allowed to bite human volunteers—two subjects being used for each species of insect. One volunteer, on whom 13 *P. papatasi* had fed developed typical sandfly fever after an incubation period of about 3½ days, while another, on whom 21 engorged one or more times, exhibited no signs of the disease. None of those bitten by either *P. irritans* or *C. pipiens* developed the disease. In the *P. irritans* tests, 23 insects fed one or more times on each of the two volunteers, while in the case of *C. pipiens*, 11 insects fed one or more times on one volunteer and 7 insects one or more times on the other. It should be noted that the five volunteers who failed to develop the disease were subsequently shown to be susceptible when they developed typical sandfly fever after an intracutaneous injection of 0.3 cc. of the infectious serum constituting the pool obtained from the original lot of naturally infected patients.

In a subsequent experiment, another lot of sandflies reared from ova in the laboratory was fed on two volunteers who were inoculated with the serum obtained from individuals with the experimentally induced illness. After suitable incubation periods, these sandflies were allowed to feed on two additional human volunteers, one of whom developed typical sandfly fever (bitten by 13 flies), while the other (bitten by 12 flies) failed to develop the disease. Thus, in two separate experiments, it was possible to demonstrate that the infectious agent which was capable of reproducing the manifestations of naturally occurring sandfly fever was also transmissible by *P. papatasi*, but not by *C. pipiens*, *P. irritans*, and in later experiments also not by *Aedes aegypti* (chart 4). It is noteworthy that other sandflies reared in the laboratory, which were not allowed to feed on infected patients, were found to be free of the virus, as demonstrated by tests on two human volunteers who were bitten by 56 and 91 flies, respectively. At least one of these two volunteers was later shown to be susceptible to the virus when he developed the disease following a parenteral inoculation of infectious serum. It should be noted here that additional experiments with *C. pipiens* also yielded negative results in three volunteers. The extrinsic incubation periods were purposely prolonged (1) to compare with the experience with yellow fever in which unfavorable mosquito hosts may become infectious after a longer extrinsic incubation period than is required for *A. aegypti*, and (2) in case occult virus was present which needed stimulation by repeated blood meals. The conclusion from these tests was that, excepting *P. papatasi*, none of the other bloodsucking insects which were tested could play important, if any, roles as vectors of this virus.

The question of interstadial or transovarial transmission of the virus was tested in the Commission laboratory, as follows: (1) *P. papatasi* larvae were allowed to ingest lyophilized virus (human serum) and the resulting adults were tested on human volunteers with negative results, and (2) *P. papatasi* hatched out in the laboratory from ova derived from parent females of proved

CHART 4.—Capacity of various bloodsucking insects to transmit phlebotomus fever



infectious capacity as late as 8 to 10 days after the infectious blood meal failed to produce the disease in human volunteers. While these experiments were not extensive, they indicated that the virus did not pass from generation to generation in all infected flies; however, it was realized that this question could not be regarded as having been settled, particularly in view of Whittingham's<sup>47</sup>

<sup>47</sup> See footnote 9(2), p. 113.



and Moshkovsky's<sup>48</sup> experiments which still left the possibility that such an event might occur occasionally.

**Attempted propagation of the virus.**—Using human serum, whose pathogenicity was established by simultaneous tests in human volunteers, inoculations were performed by the intracerebral, intranasal, intracutaneous, subcutaneous, intratesticular, and intraperitoneal routes in monkeys, young hamsters, young albino mice, wild gray mice, desert rats, rabbits, and guinea pigs. In the first series of tests, there was no suggestion of reaction in any of the animals except the hamsters, where it is probable that some infectious agent was carried for two passages before it was lost.

Two of the six hamsters which were first inoculated succumbed with nervous signs on the fifth day. One died and the other was sacrificed, and suspensions of their brains and viscera, which were bacteriologically sterile, were passaged into three new hamsters. One of these three again succumbed with similar severe nervous signs 3 days after inoculation. Although its brain and viscera were bacteriologically sterile, there was histologic evidence of acute ependymitis and meningitis as well as focal necrotic and inflammatory foci in the liver. Nevertheless, further passage into new hamsters was negative, as were also repeated inoculations of the material from the first two hamsters into six new ones, and of the original pool of acute sandfly fever serum into six additional hamsters. In addition to these tests, hamsters were also inoculated with whole blood or serum from other acute cases of natural or experimental sandfly fever as well as with a suspension of infected *P. papatasi*, but all with negative results. The total number of hamsters used in these tests was 58, and all that one can conclude is that no clinically apparent infection can be produced with regularity in these animals by the sandfly fever virus. Since no tests on human volunteers were carried out, one can say nothing about the possibility of clinically inapparent propagation of the virus in this species.

The susceptibility of white mice was also tested extensively in 74 animals, using the same material inoculated in hamsters. The results were all negative including blind passage with the brains and lungs of the inoculated mice.

Ten monkeys representing five different species were inoculated intracerebrally, intracutaneously, subcutaneously, and intraperitoneally with infectious serum or whole blood from cases of natural or experimental sandfly fever. There were three grivets (*Cercopithecus griseoviridis*), two vervets (*Cercopithecus aethiops centralis*), two red African hussars (*Cercopithecus [Erythrocebus] patas*), one *Macaca radiata* from India, and two young baboons (*Papio hamadryas*). No fever or other clinical manifestations of disease were observed in any of them. With the exception of the three grivets, which had been in Cairo for at least 1 year, and the *M. radiata*, whose history was unknown, the other monkeys were brought by plane from regions of Africa which are presumably free of sandfly fever and *P. papatasi*.

<sup>48</sup> See footnote 41, p. 134.

In view of the reports and conclusions of Shortt and others that the virus of sandfly fever had been cultivated on the chorio-allantoic membrane of embryonated eggs with the production of plaques which could be prevented by convalescent serum, special efforts were made with this method. Among twenty-two 10-day embryonated eggs inoculated in this manner with the pool of acute sandfly serum of proved potency and with the sera from five acute cases of the natural or experimental disease, all embryos survived and only one egg exhibited a single plaque on the chorio-allantoic membrane. On passage of a suspension of this membrane into four new eggs, one egg again showed an opaque zone on the chorio-allantoic membrane, but the same was found in one of three control eggs which were inoculated with the 5 percent normal chicken serum-Tyrode's solution which was used to suspend the original membrane.

Five blind passages at 4-day intervals were carried out in eighteen 8-day eggs inoculated into the allantoic sac and six passages at similar intervals in twenty-three 6- to 7-day eggs inoculated into the yolk sac. No evidence of pathogenicity for the chick embryo was observed. Inoculation of hamsters and white mice with the first and fifth passage allantoic fluid and fourth passage yolk sac yielded negative results. Negative results were also obtained when the allantoic fluid and yolk sac suspensions were used as antigens in complement fixation tests with convalescent sera from patients with the experimental disease. Thus, although volunteers were not inoculated with any of the chick embryo material, making it impossible to conclude that the virus did not multiply in the embryonated eggs, it was, nevertheless, apparent that the chick embryo could not be used either for identification of the virus or for detection of the specific antibody, as the reports of Shortt and his associates had led one to hope.

**Search for a specific or nonspecific diagnostic test.**—Precipitin, complement fixation, and hemagglutination tests were tried using the acute stage serum obtained from natural or experimental cases of the disease, or an extract of *P. papatasi* fed on experimentally infected volunteers as the antigen, and convalescent sera from natural and experimental cases as the antibody. All yielded negative results. An attempt was made to determine whether or not a skin test might be devised by testing the effect of fresh and heat-inactivated infectious sera in normal individuals and in volunteers convalescent from the experimental disease. However, no significant skin reactions were obtained in any of them. Nonspecific tests in the form of sheep cell agglutinins and cold agglutinins were also investigated with negative results.

**Preliminary observations on immunity to homologous virus.**—Two preliminary tests were carried out on the volunteers in the desert laboratory. In the experiments with various vectors, the volunteer who developed the experimental disease after being bitten by infected *P. papatasi* was found to be immune when tested with infectious serum 17 days after the onset of his fever, while five other volunteers, inoculated simultaneously with the same dose, all developed typical sandfly fever. The volunteers used in the very first

experiment on infectivity of the original pool of sandfly fever serum were each reinoculated with 0.1 cc. of the same infectious serum 14 days after the first inoculation, or 8 to 10 days after the first day of fever, and only one exhibited a rise in temperature of 1° F. 3 to 4 days after inoculation unassociated with any symptoms. However, since there were no simultaneous controls for this test, the negative results could not be regarded as conclusive, and it was evident that the question of immunity still remained to be investigated experimentally.

**Summary of work accomplished and problems requiring further study.**—Perhaps the most important achievement in this laboratory was the accumulation of a considerable amount of infectious serum in which the existence of the virus of sandfly fever was established not only by serial transmission experiments but also by the proof of its transmission by *P. papatasi*. The hope that some simple laboratory animal or embryonated eggs could serve as indicators of the presence of this virus was unfortunately dispelled by the preliminary experiments that were carried out. In addition to further attempts at adaptation of the virus in experimental animals and embryonated eggs, it was believed of the greatest importance to learn more about immunity to this virus under experimental conditions. In view of the conflicting reports concerning the immunity which follows an attack of the natural disease, it was deemed advisable to learn what immunity may result from an experimental attack of the disease when the same strain was used for challenge in individuals living in sandfly-free regions. It was also desirable to determine whether or not doses of the virus, too small to produce the disease, would prove to be immunogenic and whether or not inactive virus could produce immunity. It also seemed of interest to determine whether or not serial passage of the virus in human beings without intervention of the natural insect vector might perchance cause sufficient attenuation to permit its use for immunogenic purposes. Twenty-seven American enlisted men served as volunteers in the studies carried out in the desert laboratory.

## STUDIES ON HUMAN BEINGS IN THE UNITED STATES

Since *P. papatasi* is not present in the United States and since its importation was prohibited, it is clear why the initial, orienting experiments just reported were best carried out in the desert laboratory in Egypt. It was also clear, however, that the more extensive work involving the use of larger numbers of human subjects as well as the definitive studies on immunity could be carried out better in the United States where American civilians might become available as volunteers and where the studies on immunity would not be complicated by the question of spontaneous reinfection, perhaps inapparent infection, in nature. Accordingly, through the cooperation of the authorities of Longview State Hospital in Cincinnati, Ohio, and with the special cooperation of its medical director, Dr. Douglas Goldman, the patients in that hospital requiring some form of fever therapy, with the consent of their families or guardians, became available for tests on materials



suspected of containing virus of sandfly fever. The work was carried out by the author in his laboratories at the Children's Hospital Research Foundation and the Department of Pediatrics of the University of Cincinnati College of Medicine, Cincinnati, Ohio. In addition to the patients who were available at Longview State Hospital between October 1943 and April 1944 and again between June 1945 and the end of 1945, a number of tests were carried out on human volunteers among the prisoners of the New Jersey State Prison at Trenton, N.J., between May 1944 and May 1945.

### Isolation of Sicilian Strain of Virus and Its Identification by Cross-Immunity Tests With Middle East Strain

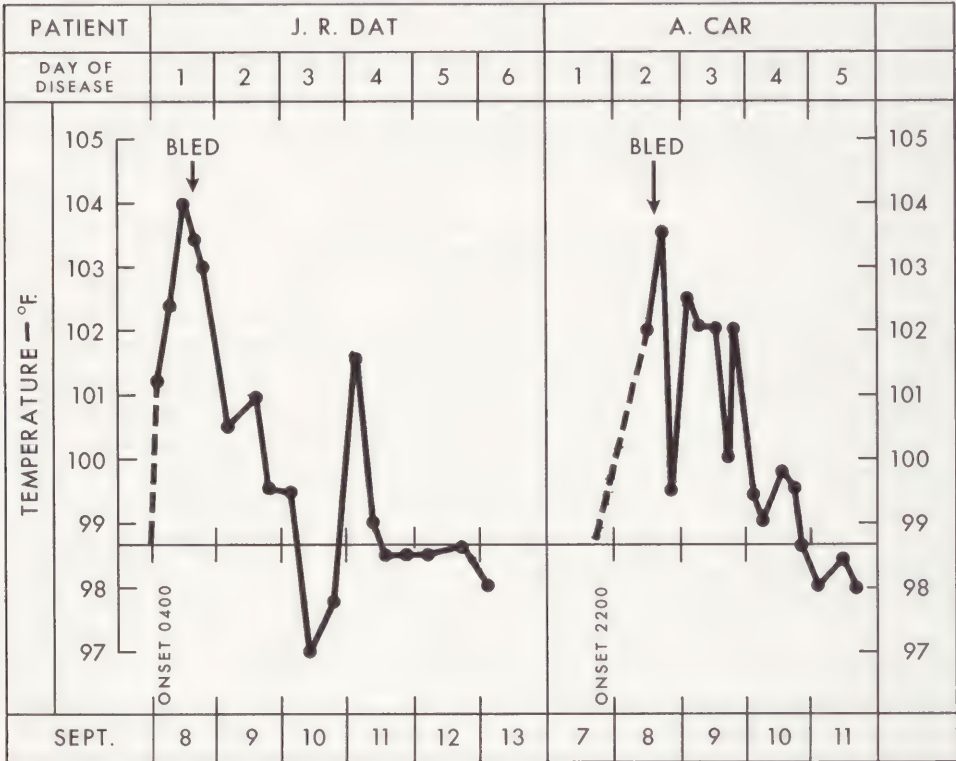
A field investigation which this author carried out during the Sicily Campaign (pp. 168-174) indicated that an estimate of approximately 8,500 cases of sandfly fever was reasonable for the period of 10 July to 3 September 1943, among the personnel of the Seventh U.S. Army.<sup>49</sup> It seemed highly desirable, therefore, to establish by laboratory methods the nature of the etiologic agent responsible for the febrile illness that was seen more often than any other disease during that period in Sicily. Accordingly, blood was obtained within 24 hours after onset from three patients who, at the time, were in the 91st Evacuation Hospital in Palermo, Sicily. The serum was at the prevailing room and outdoor temperatures for a period of about 40 hours before it reached the Commission laboratory in Cairo on 10 September, where a part of it was frozen in Dry Ice and the remainder lyophilized. These specimens were then transported to the United States in Dry Ice, and after it was learned that the subsequent clinical course of the patients from whom the blood was drawn corresponded clinically to that of sandfly fever, the serum of two of these was used for transmission tests in Cincinnati on 6 October 1943 (the temperature charts of the two donor patients are shown in chart 5).

Each of four patients at the Longview State Hospital received 0.1 cc. of serum intracutaneously and 0.75 cc. subcutaneously. All four of the recipients developed typical sandfly fever after the usual incubation periods of 3 to 4 days (for record of their temperatures, see "original subjects" in chart 6). These four patients were in turn bled within a few hours after onset of fever, and the resulting serum, stored in the frozen state in Dry Ice, constituted a fresh supply of virus for the identification of the agent responsible for the Sicilian febrile illness. The cross-immunity tests by which the Sicilian agent was identified are shown in charts 6 and 7. The first group of four subjects were tested 1 month after recovery by reinoculation with homologous Sicilian material. All four were found to be immune while four new human subjects, inoculated simultaneously, developed the disease. Fifteen days later, these original four subjects, who were thus proved to be immune to the homologous Sicilian virus, were inoculated with the Middle East strain, whose identity as

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<sup>49</sup> Report, Maj. Albert B. Sabin, MC, to Chief Surgeon, Seventh U.S. Army, Col. Daniel Franklin, MC, 7 Sept. 1943, subject: Estimate of Extent to Which Sandfly Fever Was and Is a Problem Among American Forces in Sicily.

CHART 5.—Temperature charts of original patients from whose blood the Sicilian strain of phlebotomus fever virus was isolated



a sandfly fever virus had already been established by transmission tests with *P. papatasi*. All four were again found to be immune, while four controls inoculated simultaneously developed the disease. The reverse of this test, shown in chart 7, was carried out with patients who were inoculated first with the Middle East virus, and, after they were shown to be immune to the homologous Middle East agent, they were challenged with the Sicilian virus and also turned out to be immune. Thus, it was evident that approximately 6 weeks after an attack with one or the other virus, cross-immunity was readily demonstrable. It should be noted here that similar results were obtained in subsequent cross-immunity tests, which were carried out at 4 months as well as 2 years after a single attack, indicating that by active resistance tests the two agents were indistinguishable.

Properties of the Virus

**Infectivity of the virus by different routes.**—Using serum obtained within 24 hours after onset of fever and doses of 1 cc. or more, it was found that intracutaneous or intravenous routes of inoculation produced infection in approximately 95 percent of over 100 human adults regardless of sex or color.

CHART 6.—Cross-immunity between Sicilian and Middle East strains of phlebotomus fever virus

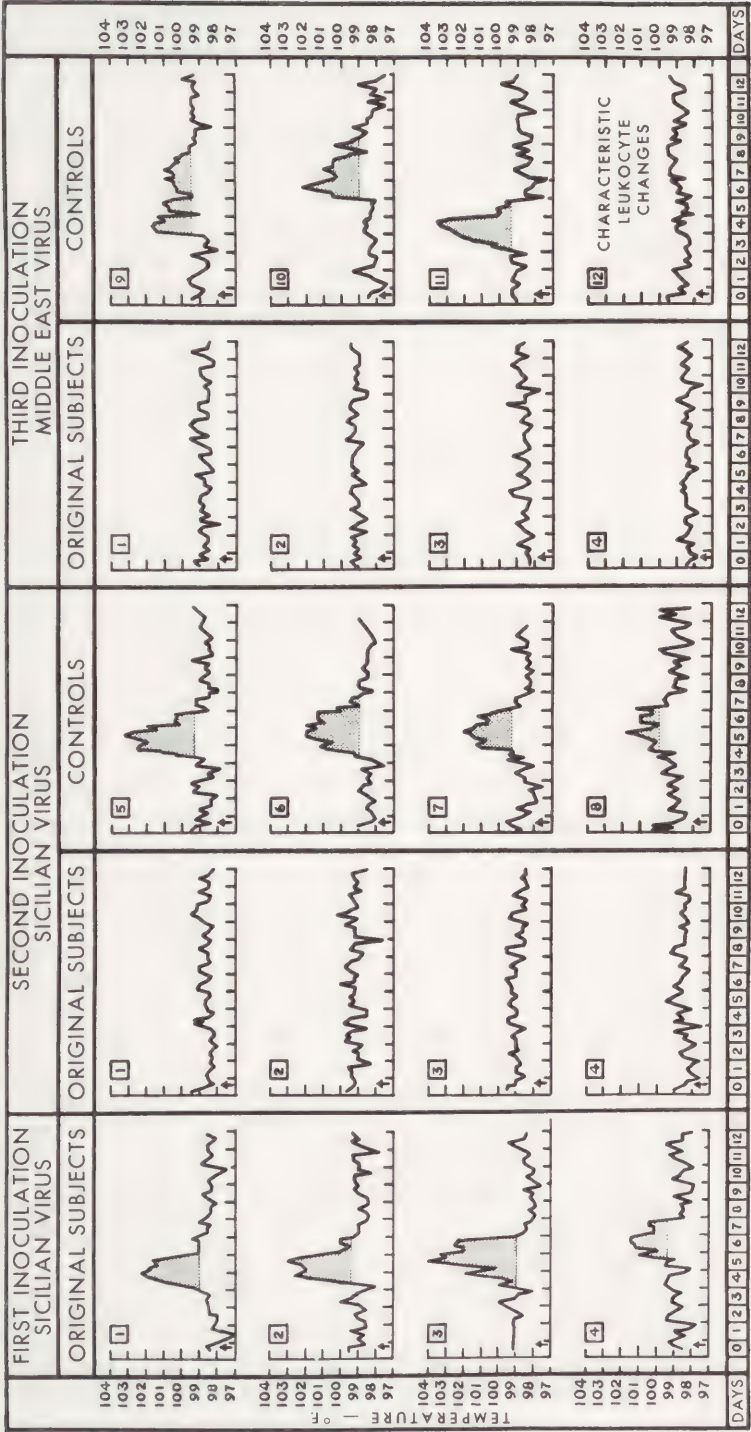
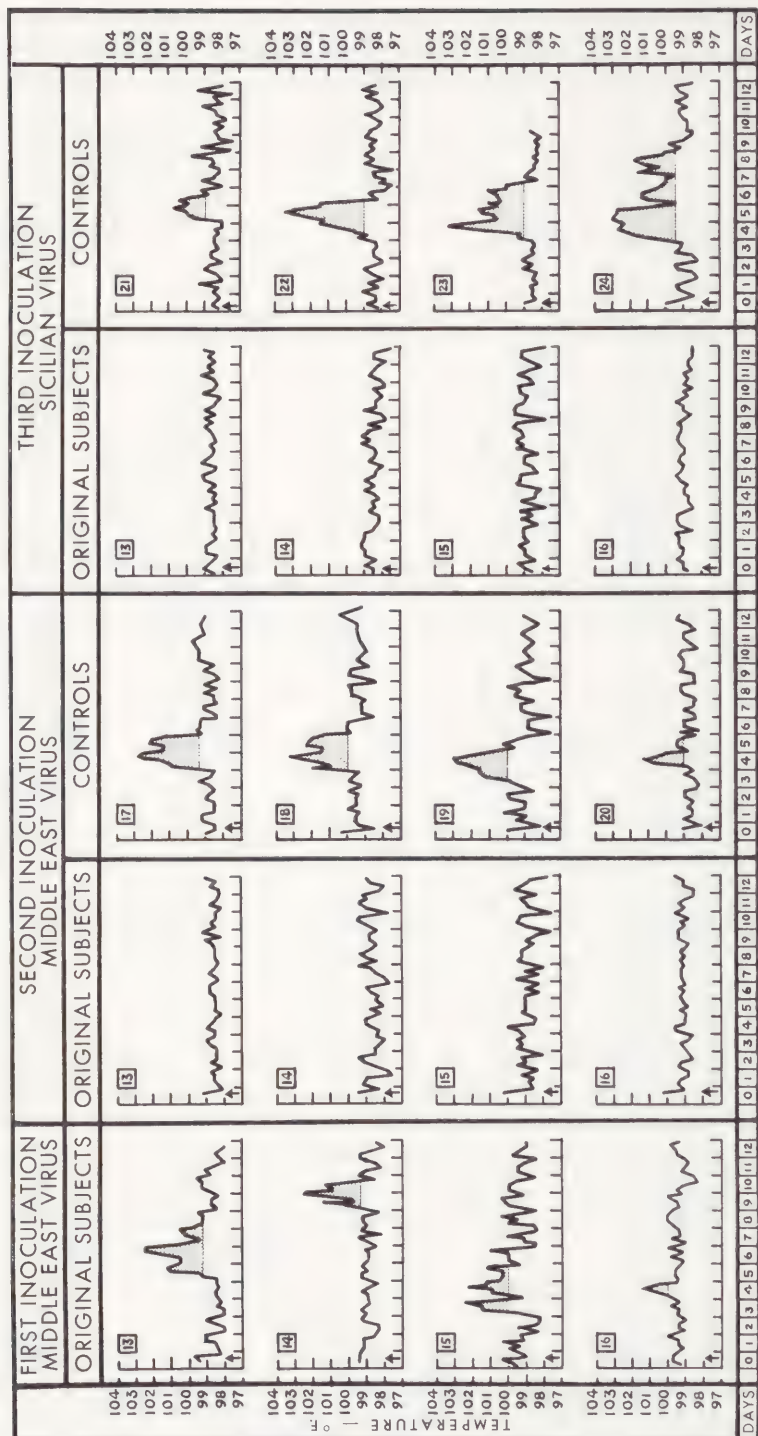




CHART 7.—Cross-immunity between Middle East and Sicilian strains of phlebotomus fever virus



During the course of experiments on filtrability of the virus, it was discovered quite by accident (when it was necessary to inject diluted serum in larger quantities by subcutaneous or intramuscular routes) that doses of virus which were infective by the intracutaneous or intravenous routes failed to produce the clinically apparent disease in 50 to 75 percent of individuals inoculated simultaneously by the subcutaneous or intramuscular routes. In two tests with the Sicilian virus, six of eight patients (75 percent) failed to develop the disease following subcutaneous or intramuscular inoculation, and in a single test with the Middle East virus, three of six patients (50 percent) failed to develop the disease following subcutaneous inoculation. The six individuals who failed to develop the disease following inoculation with the Sicilian virus were subsequently retested by the intracutaneous injection of a dose of virus which brought down all three controls, and all of the six again failed to show any signs of illness. Since it seems unlikely that so large a number would have been spontaneously resistant to begin with, it would appear possible that subcutaneous or intramuscular inoculation of the virus may have produced an inapparent infection with subsequent immunity.

**Concentration of virus in infectious serum.**—The concentration of virus in serum obtained within a few hours after onset of the fever was measured (1) by determining the minimal dose which will produce the clinical disease in human volunteers, and (2) by reinoculating those volunteers who failed to show any signs of the disease to determine whether or not the subclinical doses produced immunity. The first experiment was done with a preparation of lyophilized serum which was obtained from a human volunteer in Egypt who developed the disease after being bitten by *P. papatasi* artificially infected in the laboratory. Of three patients inoculated with 0.1 cc. intracutaneously and 0.9 cc. subcutaneously, two developed the disease. However, none of nine other patients inoculated simultaneously with 0.1, 0.01, or 0.001 cc. (three patients for each dose) by the intracutaneous route developed the clinical disease. Upon subsequent challenge, all those who remained well after the initial inoculation were proved susceptible to larger doses of the virus. In a subsequent experiment with third passage Middle East virus, using the serum of a single patient, it was found that 0.01 cc. produced the typical disease in both inoculated patients, 0.001 cc. also produced a clinically recognizable illness in a single patient, while 0.0001 cc. failed to produce the disease in one patient. Although this represents a rather inadequate titration, it would appear that in this particular serum the minimum infective dose may have been 0.001 cc. However, in the third experiment with Middle East virus using seventh passage material from a single patient, the serum having been frozen in Dry Ice for 8 months, it was found that only one of four patients inoculated with 1 cc. intracutaneously developed the disease. A systematic titration was not carried out with the Sicilian strain of virus; however, of 45 individuals who received 1 cc. intracutaneously (virus represented by serum derived either from natural cases of the disease or from human subjects up to six experimental passages), 43 developed clinically apparent disease. All nine individuals who received 1.5

to 2 cc. of various passages of the Sicilian strain developed the clinical disease, and two of three patients who were inoculated with 0.5 cc. of Sicilian virus developed the disease. During the gradocol membrane filtration tests, part of the pool which was found to be infective with regularity in amounts of 1 cc. was also tested in smaller doses, two patients being inoculated with 0.0001 cc. and another two patients with 0.00001 cc., but none developed the illness. In subsequent tests for susceptibility by inoculation of larger amounts of the same virus, all four patients developed typical experimental sandfly fever. Thus, it can be said that the Sicilian virus also does not have a potency as high as 10,000 minimum infective doses per cubic centimeter of serum.

An interesting phenomenon which may represent a difference in the behavior of sandfly fever virus in American Negroes was encountered during the course of this work. Although it was found that Negroes were as susceptible as white people when inoculated with serum derived from white individuals with sandfly fever, it was not possible to obtain passage when the serum of Negroes with the disease was used. In three different experiments using 1 cc. amounts of serum from three different Negroes, negative results were obtained. When the volunteers used in these tests were subsequently inoculated with serum from white donors, all developed sandfly fever, indicating that they were susceptible. Since amounts larger than 1 cc. were not tested, one cannot say that the virus might not have been present in smaller concentration in the blood of Negroes who developed experimental sandfly fever. However, the results do suggest that the virus may perhaps not propagate to as high a level in Negroes as it does in white individuals. Since it had been demonstrated that the sandfly fever virus can be maintained in the lyophilized state or frozen in Dry Ice for a period of at least 4 years, it is not likely that the manner of storage of the serum seriously affected the results that were obtained.

**Particle size of the virus.**—Two experiments were carried out with the Sicilian strain of sandfly fever virus in an attempt to determine the particle size by means of filtration through gradocol membranes. Twenty-six human subjects were used for the tests, and the results are shown in table 23. The first test was unsatisfactory because the inoculations were given by the subcutaneous and intramuscular routes before it was realized that these routes were less suitable than the intracutaneous. However, the second experiment yielded clean-cut results in that all 10 volunteers inoculated intracutaneously and intravenously with either the diluted, unfiltered serum or the filtrates from the 600, 400, 310, and 207  $m\mu$  membranes developed typical sandfly fever, while the two patients inoculated with somewhat larger doses of the filtrate from the 101  $m\mu$  membrane both failed to develop any signs of illness or changes in the leukocytes. Although it is possible that one of these two patients may have had an inapparent infection since he failed to develop the disease on challenge with active virus later on, it is, nevertheless, evident that the average pore diameter of the endpoint membrane is in the range of 101  $m\mu$ . If one assumes that the 101  $m\mu$  membrane represents the filtration endpoint, the particle size of the virus may be estimated at 40 to 60  $m\mu$ , according to Elford's



TABLE 23.—*Filtration of sandfly fever virus through gradocol membranes*

Experiment	Portion tested	Amount injected (cc.)		Patient	Result	Result of subsequent challenge with virus intracutaneously
Pool of passage I serum, diluted 1:5 in saline, and centrifuged at 1,500 r.p.m. (all filtrates inoculated subcutaneously and intramuscularly).	Centrifuged, unfiltered..	5		D.....	Negative.....	Negative.
	770 m $\mu$ filtrate.....	5		S.....	do.....	Do.
	309 m $\mu$ filtrate.....	5		A.....	Sandfly fever....	
	203 m $\mu$ filtrate.....	5		B.....	Negative.....	Do.
	101 m $\mu$ filtrate.....	5		Al.....	do.....	Sandfly fever.
	75 m $\mu$ filtrate.....	5		K.....	do.....	Do.
		5		Br.....	do.....	Do.
		5		Do.....	do.....	Negative.
		5		Ba.....	do.....	Do.
		5		Di.....	do.....	Sandfly fever.
Pool of passage V sera, diluted 1:4 in saline, and centrifuged at 2,000 r.p.m. for 15 minutes.	50 m $\mu$ filtrate.....	10		C.....	do.....	Do.
				W.....	3-day fever leukocytosis pharyngitis.	Do.
				H.....	Negative.....	Do.
				F.....	do.....	Do.
		cc.	route			
	Centrifuged, unfiltered..	2	i. cut.	C.....	Sandfly fever....	
		6	i. ven.	CF.....	do.....	
	600 m $\mu$ filtrate.....	2	i. cut.	CL.....	do.....	
		6	i. ven.	P.....	do.....	
	400 m $\mu$ filtrate.....	2	i. cut.	Bi.....	do.....	
		6	i. ven.	Cr.....	do.....	
	310 m $\mu$ filtrate.....	2	i. cut.	S.....	do.....	
		6	i. ven.	M.....	do.....	
	207 m $\mu$ filtrate.....	2	i. cut.	L.....	do.....	
		6	i. ven.	Br <sup>1</sup> .....	do.....	
	101 m $\mu$ filtrate.....	2	i. cut.	T.....	Negative.....	Sandfly fever.
		10	i. ven.	Mi.....	do.....	Negative.

<sup>1</sup> Serum obtained from this patient at onset of fever produced typical sandfly fever in two other patients.

formula. However, it must be kept in mind that the concentration of virus in the serum used for filtration was not very great. In addition to the controls shown in table 22, three other patients were each inoculated intracutaneously with 0.5 cc. of the same pool, and two of the three developed typical sandfly fever. However, four other subjects inoculated with 0.0001 cc. or 0.00001 cc. of the same pool failed to develop the disease and also failed to develop immunity to subsequent challenge. Thus, it would appear that the concentration of virus, although not precisely known, was certainly less than 10,000 M.I.D. (minimum infective dose) per cubic centimeter. Since it is known that the amount of virus contained in the material that is filtered can influence the filtration endpoint, one would have to conclude that while the particle size of the sandfly fever virus is probably not greater than 40 to 60 m $\mu$ , there is a possibility that it may be smaller.

**Further tests in animals.**—During the course of the work with this virus in the United States, additional tests were carried out with sera of proved infectivity for human beings on the following animals: Infant mice, cotton rats,

hamsters, and monkeys. Because of the questionable results obtained in several hamsters in Egypt, suspensions of the brains and viscera of those hamsters, which had been stored in Dry Ice and transported from Egypt to the United States, were inoculated into six hamsters, but all remained well. An additional test on hamsters was carried out with the fourth human passage of the Sicilian strain of virus; the serum was injected in six young animals by the intracerebral, intracutaneous, intraperitoneal, and intratesticular routes, but all remained well. Mice were inoculated with undiluted serum, serum diluted 1:100, and also with the sediment from ultracentrifuged serum taken up in  $\frac{1}{50}$  of the original volume. Mice varying in age from 10 days to 4 weeks were inoculated by the intracerebral and the intraperitoneal routes, but all remained well. On several occasions, when mice presented questionable signs or died after a period of 13 or 14 days, passages were performed but with negative results. The sera which was used for these tests represented some which had had only one passage from the natural disease, as well as others which had had seven serial passages in human volunteers. Six cotton rats inoculated with first passage Sicilian virus by the intracerebral, subcutaneous, and intraperitoneal routes remained well. It should be noted, however, that in none of these experiments was material from any of the animals tested in human volunteers to determine whether or not the virus might have undergone inapparent multiplication.

In view of the fact that Shortt and his associates believed that they had transmitted the virus of sandfly fever to monkeys, a special experiment was undertaken with these animals. The Sicilian virus represented by a pool of passage I human serum was inoculated simultaneously into patients and into three rhesus monkeys. Each monkey received a total of 6 cc. of serum—1 cc. by the intracerebral route, 0.1 cc. intracutaneously, 0.9 cc. subcutaneously, and 4 cc. intraperitoneally. None of the three monkeys developed fever or showed any other clinical evidence of disease. However, they were bled at different intervals, and the serum obtained 3 and 4 days after inoculation was subinoculated in two patients. It is noteworthy that while neither of the two patients exhibited anything that the experienced investigator could have interpreted as sandfly fever, each of them, nevertheless, developed a febrile illness, one on the 10th day and the other on the 11th day, associated with generalized malaise and joint pains. However, the leukocyte changes which are characteristically present in sandfly fever did not develop in either of these two patients. Clinically, it appeared more likely that the reaction in these patients was due to serum sickness resulting from the inoculation of the monkey serum. Approximately 4 weeks later, these patients were inoculated with sandfly fever virus and both of them developed typically severe forms of experimental sandfly fever, thus confirming the original clinical diagnosis of serum sickness and indicating that no virus was present in the blood of monkeys 3 and 4 days after inoculation of human sandfly fever virus. No evidence was, therefore, obtained that the sandfly fever virus was either pathogenic for rhesus monkeys or indeed multiplied inapparently during the period tested.

Although the work was halted because of the pressure of other investigations, it appeared that further experiments with newborn and 1- and 2-day-old rodents, particularly mice, would appear to be worthwhile not only in an attempt to establish the virus in a small experimental animal but more especially to determine whether the sandfly fever virus may be propagating inapparently. It would be desirable to test such material passaged in newborn rodents not only for pathogenicity in human beings but even more especially for the capacity to produce immunity to unmodified human virus should it turn out to be nonpathogenic.

**Further cultivation attempts in embryonated eggs.**—Although the experiments carried out in the Middle East laboratory indicated that no specific antigen suitable for complement fixation tests could be obtained from eggs inoculated with human serum containing sandfly fever virus, it was, nevertheless, desirable to determine whether or not inapparent multiplication of the virus may occur in embryonated eggs, as determined by subinoculation in human volunteers. The tests which were carried out in the United States are summarized in table 24. It may be seen that among the nine human volunteers inoculated with various types of chick embryo material, two developed febrile reactions 12 and 13 days after inoculation, but it was possible to show that in neither one of those instances was the fever due to infection with sandfly fever virus, because subsequent challenge produced the typical disease in both volunteers. Although in one test, two of four volunteers inoculated with fourth egg passage material failed to develop sandfly fever on challenge, it would appear more likely from the other results that these two human subjects might have represented individuals who were resistant to this virus to begin with. It was necessary to conclude from these tests that there was no evidence that the sandfly virus could multiply in chick embryos inoculated by the various routes that were tried. Accordingly, it was not possible to obtain confirmation of the conclusions reached by Shortt and his coworkers. It may also be stated here that an attempt was made to grow the sandfly fever virus in cultures containing minced mouse embryo brain or minced whole mouse embryo. Inoculation of the third passage culture material in human volunteers yielded negative results.

**Further tests with *A. aegypti*.**—Although a preliminary test carried out in the Middle East laboratory indicated that *A. aegypti* mosquitoes were unable to transmit the virus of sandfly fever, it was desirable to determine beyond doubt, as far as it may be possible to do so, whether *A. aegypti* mosquitoes in large numbers and after varying periods of extrinsic incubation can or cannot transmit this virus. In view of the hypothesis that had been forwarded by some investigators<sup>50</sup> that the sandfly fever and dengue viruses may belong to one group, it was particularly important to determine this point with great care. Three experiments were carried out with human volunteers in the United States, with the assistance of Lt. (later Capt.) William G. Jahnes, SnC. Large numbers of freshly emerged mosquitoes were allowed to feed on

<sup>50</sup> Van Rooyen, C. E., and Rhodes, A. J.: *Virus Diseases of Man*. London: Oxford University Press, 1940, p. 516.



TABLE 24.—*Human tests with chick embryo "cultures" initiated with sandfly fever virus of proved potency*

Inoculum for embryonated eggs	Site of inoculation, age of embryo, and passage	Material tested in human subjects	Subject	Result of inoculation	Result of subsequent challenge
Middle East strain, human passage III serum.	Embryo and yolk sac, 9-day eggs, passaged at 4-day intervals.	4th egg passage, whole embryo, 2 cc., 20 percent suspension, intracutaneous.	K-----	Negative-----	Negative. <sup>1</sup>
			B-----	...do.-----	Do. <sup>1</sup>
			A-----	...do.-----	Sandfly fever.
			S-----	...do.-----	Do.
		3d egg passage, whole embryo, 2 cc., 20 percent suspension, intracutaneous.	F-----	4-day fever with pharyngitis plus leukocytosis 12 days after inoculation.	Do.
Sicilian strain, pool of human passage V sera.	...do.-----	5th egg passage whole embryo, 2 cc., 20 percent suspension, intracutaneous.	G-----	Negative-----	Do.
			Bo-----	1-day fever 13 days after inoculation; no leukocyte changes.	Do.
			Su-----	Negative-----	Do.
Sicilian strain, pool of human passage VII sera.	Chorio-allantoic membrane, 10-day eggs.	3d passage, chorio allantoic membrane suspension, 1 cc.	M-----	...do.-----	Not tested.

<sup>1</sup> Two controls inoculated simultaneously developed the disease.

human volunteers during the first 24 hours after onset of fever during the experimental disease. At the time the mosquitoes fed on these volunteers, blood was taken in each instance to determine, by subinoculation in other volunteers, that infective virus was actually present at the time of the biting. One experiment was carried out with the Middle East virus and two tests were carried out with the Sicilian strain of the virus. Mosquitoes which had taken blood meals from infected individuals were allowed to bite new volunteers after extrinsic incubation periods varying from 6 to 22 days. Six human volunteers were bitten by hundreds of mosquitoes which had taken blood meals from infected human beings at the time when their blood was shown to contain the virus, but none of them developed sandfly fever. The susceptibility of all these volunteers was subsequently demonstrated when they developed the typical experimental disease following inoculation of serum from the very donors on which the mosquitoes had obtained their blood meals. This unequivocal demonstration of the inability of *A. aegypti* to act as a vector of the virus of sandfly fever became an important tool in the differentiation of this virus from that of dengue.

**Tests for virus in cerebrospinal fluid and in blood.**—Observations on more than 100 cases of the experimentally produced disease indicated that the duration of fever in different individuals may vary from part of 1 day to 9 days, although the 2-, 3-, and 4-day periods constituted 85 percent of the total (chart 8). Multiple cycles of fever (chart 9) after a single inoculation of virus were observed in four patients. Subinoculation experiments made it possible to show that the virus was present in the blood 24 hours before the

CHART 8.—Various types of fever produced by experimental inoculation of phlebotomus fever virus in human beings

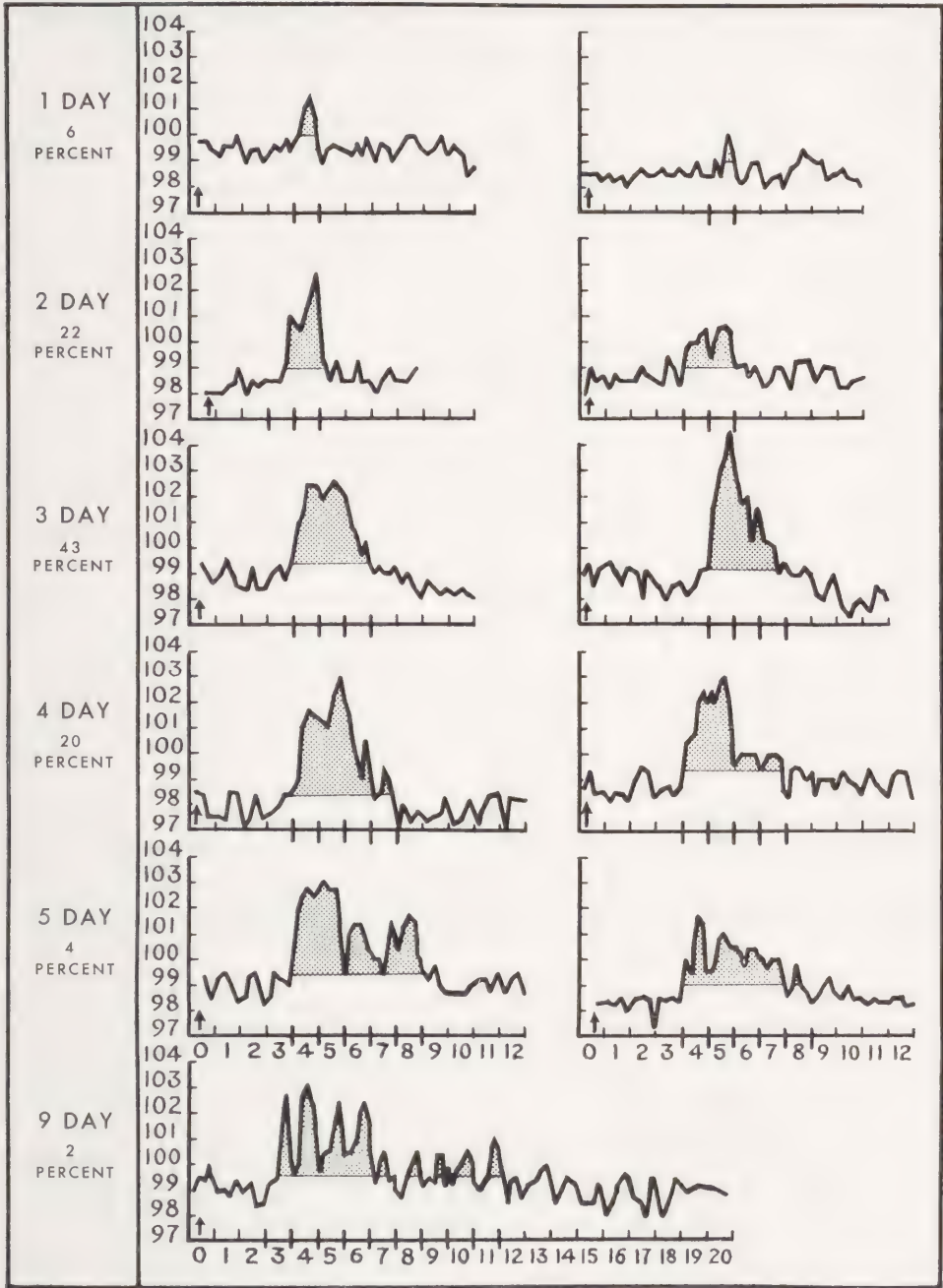
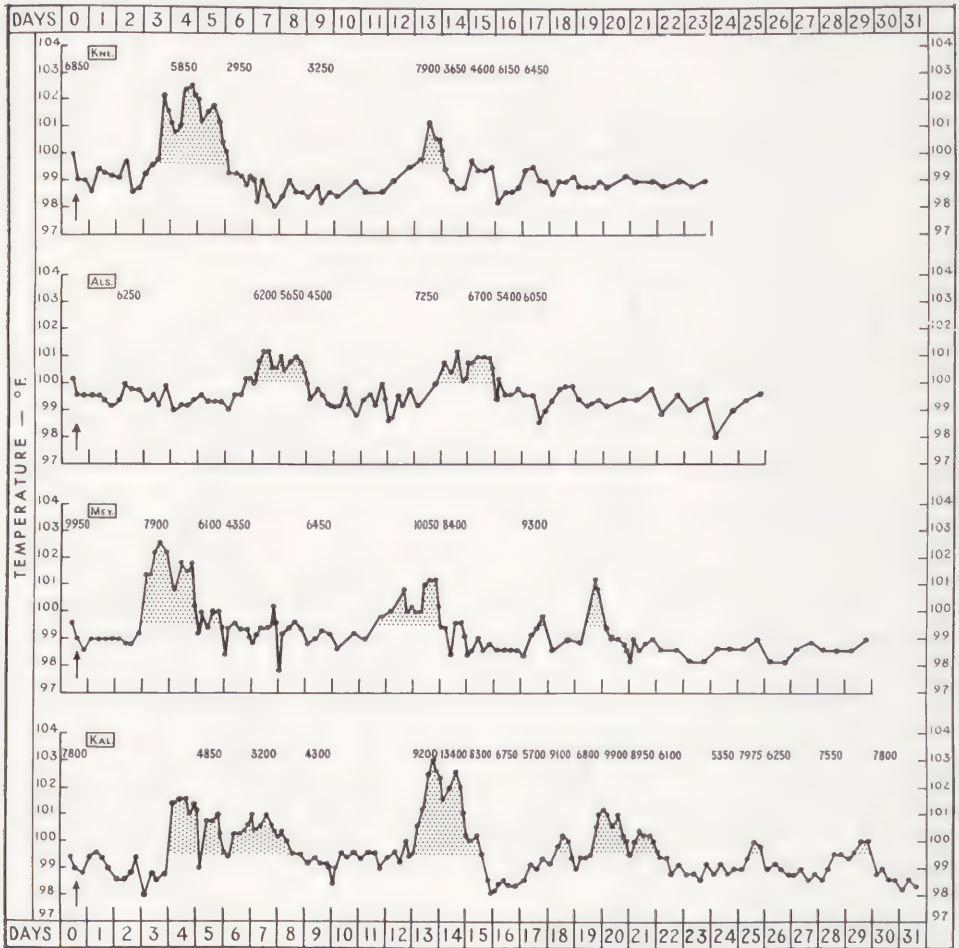


CHART 9.—Multiple cycles of fever after single injection of phlebotomus fever virus in human beings



onset of the fever but could not be demonstrated in the blood of several patients 48 to 54 hours after onset of the fever. No explanation was found for the multiple cycles of fever. Since no virus could be recovered from the blood during the periods of recurring fever, the relapses could not be explained on the basis of recurring viremia.

Cerebrospinal fluid was obtained from five of the American volunteers during the work in Egypt. No pleocytosis or other abnormalities were found in those fluids, and part of each fluid was lyophilized and the remainder frozen in Dry Ice and transported to the United States. Two patients were inoculated with the pool of these cerebrospinal fluids, each receiving 2 cc. intracutaneously and 15 cc. intravenously. Neither developed the fever or the leukocyte changes characteristic of sandfly fever, and both were subsequently



shown to be susceptible to an inoculation of the virus. It is noteworthy that the serum of the same volunteers, lyophilized and frozen in the same manner and transported to the United States, was also tested on human volunteers and proved to be infective.

**Storage and maintenance of infectivity of the virus.**—Since so much work was involved in establishing the identity of an authentic strain of the virus of sandfly fever, it was of considerable importance to determine whether or not and under what conditions it may be possible to preserve this virus. Accordingly, at various intervals, portions of human serum maintained in the frozen state in Dry Ice, as well as portions of serum which had been lyophilized and then stored in an ordinary refrigerator, were tested in human volunteers. When the work on sandfly fever was terminated at the end of 1945, it was found that the second passage pool of the Sicilian strain, which was frozen in Dry Ice on 30 November 1943, still produced the disease in both patients receiving 2 cc. of the serum intracutaneously on 10 October 1945. Thus, it was clear that the virus persisted for at least 2 years in that state. Lyophilized virus tested at the end of 6 months was found to be active. In subsequent years, an opportunity presented itself to test some of the lyophilized and frozen virus on children with nephrosis as part of a trial therapeutic study, and it was possible to show that the virus remained active after a period of storage of at least 5 years. These strains of virus are still available in the author's laboratory in both the frozen and the lyophilized states. It is hoped that virus preserved in this manner may prove useful for any future comparative purposes or studies that may be contemplated.

**Tests for neutralizing antibodies.**—Determination of the presence or absence of neutralizing antibodies in sandfly fever was desirable not only for academic reasons but also (1) to find a serological means for the identification of the virus or its various types, and (2) to establish whether or not active immunity could be produced by the inoculation of neutral serum-virus mixtures. Two tests were carried out, and the results are summarized in table 25. The hyperimmune serum used in these tests was derived from four patients who recovered from an experimental attack of the disease following inoculation of the Sicilian strain of the virus. Four weeks later, they were reinoculated with the Sicilian strain and were found to be immune. Two weeks after that, they received an inoculation of the Middle East strain of the virus of proved potency, and they were again resistant. Two weeks after this second challenge, or 8 weeks after the first inoculation of virus, they were all bled, and their serum constituted the hyperimmune serum used in these tests. These results shown in table 25 indicate that in neither test was complete neutralization of the virus obtained. It is possible, however, that a certain degree of neutralization did occur, because in each of the tests there was one subject who failed to develop any signs of illness or leukocyte changes following inoculation of the immune serum-virus mixtures and yet, on challenge, subsequently developed typical sandfly fever. These challenge tests indicated not only that the subjects were originally susceptible but, also, incidentally, that the inoculation of the hyper-

immune serum-virus mixture does not lead to the development of active resistance to the virus.

TABLE 25.—*Tests for neutralizing antibodies*

Experiment	Strain of virus	Mixture inoculated	Subject	Result	Result of subsequent challenge
1-----	Middle East-----	Virus only, 1 cc-----	1-----	Sandfly fever-----	Sandfly fever.
			2-----	do-----	
		Virus (1 cc.) plus hyper-immune serum (1 cc.) 1.5 hours at 23° C.	3-----	do-----	
			4-----	Negative-----	
2-----	Sicilian-----	Virus only, 0.5 cc-----	5-----	Sandfly fever-----	Do. Negative.
			6-----	do-----	
		Virus (0.5 cc.) plus hyper-immune serum (1 cc.) 2.3 hours at 23° C.	7-----	Negative-----	
			8-----	do-----	
			9-----	do-----	

## PERSISTENCE OF IMMUNITY FOLLOWING A SINGLE ATTACK OF SANDFLY FEVER

Various observations recorded in the literature concerning persistence of immunity to sandfly fever and recurrence of the disease seemed to be confusing and contradictory. On the one hand, there are reports of multiple attacks, occasionally also during one season, and on the other, there are numerous observations that so-called "salted" troops (that is, troops that had once experienced an epidemic of sandfly fever) proved to be resistant during subsequent seasons, at a time when newly arrived troops were contracting the disease. Whether or not a single attack of the disease in residents in a sandfly fever area had to be fortified by repeated exposures to the virus in order to acquire lasting immunity was not known. The studies which were carried out in the United States, a country free of the disease, made it possible to determine the immunogenic effect of a single experimental attack of sandfly fever when the same strain of virus, or an immunologically closely related or identical strain, was used for challenge.

The data summarized in table 26 indicate that the 8 volunteers tested 1 month after infection and the 10 volunteers tested 4 months after infection all remained well, while control patients inoculated simultaneously with the same virus developed the disease. In a test carried out 2 years after a single attack of the disease, three of the four patients remained entirely well, showing neither fever, symptoms, nor changes in the leukocytes, while the fourth patient may have experienced a very mild, modified form of the infection. Although this patient (Mc) had no subjective complaints, he, nevertheless, exhibited a rise in temperature of 1° F. for a period of about 24 hours 6 days after inoculation. This was associated with changes in the leukocytes characteristic of this infection. It is regrettable that the presence of reinfection in this individual

was not proved or disproved by transmission of the disease to others. However, it would appear that in the majority of individuals immunity to reinfection with the same immunologic type of sandfly fever virus was present for a period of at least 2 years. If the events which occurred in the fourth patient tested at 2 years were, in effect, due to reinfection it may perhaps indicate that as immunity wanes reinforcement might be possible by essentially subclinical infections.

Tests on two American physicians who had resided in Palestine for varying periods yielded interesting results with reference to the persistence of immunity. Both of them had lived in Cincinnati before 1932, and both gave histories of two previous attacks of the disease during a period of residence in Palestine.

Dr. Helen Glueck had her first attack during the summer of 1932, 5 days after she landed in Palestine. She returned to the United States in 1934 and lived there until 1937 when she again went to Palestine. After a trip to Syria in August 1937, she experienced a febrile illness of 2 days' duration associated with leukopenia which was again diagnosed as sandfly fever; that is, a second attack of the disease after an interval of 5 years. She returned to the United States in 1939 and volunteered for an immunity test in 1943; that is, 6 years after the presumable second attack of sandfly fever. She was inoculated with the Middle East strain of virus (1 cc. of passage III human serum intracutaneously) and after an incubation period of 3 days developed a typical, moderately severe attack of sandfly fever, associated with characteristic leukocyte changes.

Dr. Irwin Dunskey experienced his first attack of sandfly fever in Jerusalem during the summer of 1934, and another similar attack, of somewhat diminished severity, during the summer of 1935. He returned to the United States in 1936, where he resided continuously until he volunteered for an immunity test in November 1943; that is, 8 years after the last presumable attack. He received the same virus and dose which was administered on the same day to Dr. Glueck and three previously uninoculated patients. Three days after inoculation, he became mildly ill (aching in the neck, "giddy," and mild intermittent abdominal distress) for a period of about 4 hours during which time his temperature was 1.5° F. above his normal level for that time of day. Although the total number of leukocytes dropped from 6,900 to 4,400, there was no associated change in the differential formula.

The history of these two physicians shows how difficult it is to interpret the significance of presumably repeated attacks in individual patients, when one is dealing with a disease for which there is no specific clinical identifying sign or laboratory test. Thus, one is faced with several possible explanations. It is possible (1) that one or both attacks of the natural disease diagnosed as sandfly fever were not sandfly fever, (2) that immunity to sandfly fever may not persist, or (3) that multiple immunologic types of the virus may be involved.



TABLE 26.—*Persistence of immunity to homologous type of sandfly fever virus in human subjects residing in the United States*

Interval between experimental attack and challenge	Virus used for challenge	Virus previously inoculated	Subject	Result
1 month-----	Sicilian, passage I, 1 cc., intracutaneous.	None-----	J-----	Sandfly fever.
			R-----	Do.
		Sicilian-----	I-----	Remained well.
			W-----	Do.
			M-----	Do.
			Ri-----	Do.
	Middle East, passage II, 1 cc., intracutaneous.	None-----	Mc-----	Sandfly fever.
			C-----	Do.
			B-----	No fever, but characteristic leukocyte changes and symptoms.
		Middle East-----	Ca-----	Remained well.
			G-----	Do.
			Wo-----	Do.
			Br-----	Do.
4 months-----	Sicilian, passage V, 0.5 cc., for controls, 1 cc., for convalescents.	None-----	Im-----	Sandfly fever.
			Ro-----	Do.
		Sicilian-----	A-----	Remained well.
			L-----	Do.
			F-----	Do.
			Mu-----	Do.
			V-----	Do.
			Ra-----	Do.
		Middle East-----	D-----	Do.
			E-----	Do.
			Wa-----	Do.
			Me-----	Do.
			P-----	Sandfly fever.
2 years-----	Sicilian, passage II, 2 cc., intracutaneous.	None-----	Mea-----	Do.
			O-----	Remained well.
		Sicilian-----	Be-----	Do.
			C-----	Do.
			Mc-----	Modified sandfly (?)
		Middle East-----		1° F. above normal for 24 hours, 6 days after inoculation, associated with characteristic leukocyte changes.

LACK OF IMMUNOLOGIC RELATIONSHIP BETWEEN SANDFLY FEVER AND DENGUE

There was a tendency on the part of Van Rooyen and Rhodes to regard dengue, sandfly fever, and yellow fever as belonging to one group of agents. It had already been demonstrated in the present studies that sandfly fever virus could not be transmitted by *A. aegypti* and, thus, differed very definitely from the viruses of dengue and yellow fever. Tests recorded in table 27 show that not even partial cross-immunity could be demonstrated between the viruses of dengue and sandfly fever. Patients who had recovered from infections with either the Middle East or the Sicilian strain of sandfly fever virus developed typical, unmodified dengue following inoculation of human dengue serum. Similarly, the disease which following inoculation with sandfly fever virus was in no way modified when it occurred in an individual who had recovered from dengue.

TABLE 27.—*Immunologic relationship between sandfly fever and dengue*

Virus inoculated	Virus previously inoculated	Interval (weeks)	Subject	Result
Dengue, Hawaii (from natural cases).	None-----		{S-----	Typical dengue.
			{T-----	Do.
	Middle East sandfly-	{10	Lu-----	Do.
		{10	W-----	Do.
		{8	C-----	Do.
	Sicilian sandfly-----	{20	}Le-----	Do.
		{2		
Sandfly, Sicilian-----	Dengue, Hawaii-----	18	H-----	Typical sandfly.

IMMUNOGENIC ACTIVITY OF VIRUS IRRADIATED WITH ULTRAVIOLET LIGHT

As regards the attempts to produce active immunity in susceptible human beings, the results described thus far indicate (1) that subinfective doses inoculated intracutaneously or intravenously failed to produce immunity to larger amounts of virus; (2) that while the intramuscular and subcutaneous injection of infective amounts of virus seemingly frequently led to the development of an inapparent infection with subsequent immunity, this procedure was impracticable since approximately 50 percent of those inoculated might develop the disease; and (3) that virus passaged in chick embryos or mouse-embryo cultures failed to produce the disease and also failed to produce immunity. Accordingly, it was of particular interest to determine whether or not inactivation of the virus by some mild means, such as irradiation with ultraviolet

light, might abolish its infectivity without loss of immunogenic capacity. The results of the tests with the Middle East and Sicilian strains of the virus on 26 patients are shown in table 28. It may be seen that with the particular apparatus used for irradiation the effect on infectivity was highly irregular. Thus, in the experiment with the Middle East virus, all four patients inoculated with the unirradiated virus developed sandfly fever, while five of the six patients inoculated with the same material irradiated for either 15 or 30 minutes failed to develop the disease. The one individual who did develop sandfly fever was inoculated with serum irradiated for 30 minutes. In the experiment with the Sicilian virus, 4 of 5 patients inoculated with the unirradiated virus developed the disease, while only 7 of 13 inoculated with the same serum irradiated for either 15, 35, or 60 minutes developed the disease. It is worth noting that increasing the time of irradiation up to 60 minutes failed to abolish the

TABLE 28.—*Effect of irradiation with ultraviolet light on infectivity and immunogenic capacity of sandfly fever virus contained in human serum*

Strain of virus	Experiment date	Time of irradiation (minutes)	Inoculum	Subject	Result	Result of subsequent challenge <sup>1</sup>
Middle East pool of human passage V sera.	24 Nov. 1943	0	1 cc., intracutaneous.	E..... R.....	Sandfly fever..... No fever but typical leukocyte response.	Negative. Do. Do.
		15	do.....	M..... L.....	Negative..... do.....	
		30	do.....	Mu..... Me.....	do..... Sandfly fever.....	
	8 Dec. 1943	0	do.....	K..... G.....	do..... do.....	
		15	do.....	A..... S.....	Negative..... do.....	
				La..... Q.....	Sandfly fever..... No fever but typical leukocyte response.	
Sicilian pool of human passage III sera.	18 Jan. 1944	0	do.....	Sa..... Gr..... T..... H.....	Negative..... Sandfly fever..... do..... Negative.....	Negative. Do. Negative. Negative.
		15	do.....	D..... B.....	do..... Sandfly fever.....	
		15	do.....	H.A..... C.....	do..... do.....	
	24 Jan. 1944	35	do.....	Co..... H.V..... W..... Bo.....	Negative..... do..... Sandfly fever..... do.....	
Sicilian pool of human passage IV sera.	2 Feb. 1944	0	do.....	Br..... Ri..... P..... Gre.....	do..... do..... Negative..... do.....	Negative. Do. Negative. Do.
		60	do.....			

<sup>1</sup> In the Sicilian virus group, five controls inoculated simultaneously with the same dose of virus given to the seven subjects (Sa, H, D, Co, H.V., P, and Gre) for challenge, all developed typical sandfly fever; in the Middle East group, of four controls inoculated simultaneously with the same dose of virus given to the five subjects (M, L, Mu, A, S), three developed typical sandfly fever.



infectivity. However, of the 11 individuals inoculated with the irradiated serum who failed to develop the disease, all were resistant on subsequent challenge with virus of proved infectivity in simultaneous tests. Since subinfective amounts of unirradiated virus were not found to be capable of producing immunity, and since it seems improbable that 11 resistant individuals were encountered in these tests, it would appear that after irradiation by ultraviolet light for a period insufficient completely to destroy the virus, subinfective amounts may, nevertheless, be immunogenic. It was intended to repeat these experiments during the latter part of 1944, using a different machine for ultraviolet irradiation, but the difficulty was encountered that the serum obtained from volunteers who developed typical sandfly fever proved to be noninfectious in amounts of 1 cc. It was not realized until considerably later that the use of Negro volunteers was probably responsible for yielding serum which either was of a very low infectivity or was completely noninfective. As matters stand now, no conclusive results are available, but the data are sufficiently interesting to warrant repetition.

### STUDIES ON AN IMMUNOLOGICALLY DISTINCT SANDFLY FEVERLIKE VIRUS IN NAPLES, 1944

The incidence of sandfly fever among U.S. troops in Italy in 1944 (pp. 120-122) was high. In connection with a study carried out by Maj. Marshall Hertig, SnC, and Lt. Col. Ross L. Gauld, MC, of an outbreak among Allied Force Headquarters personnel, a number of sera were collected in July 1944, by Capt. (later Maj.) Frederick C. Robbins, MC, 15th Medical General Laboratory, at the suggestion of Col. William S. Stone, MC, NATOUSA (North African Theater of Operations, U.S. Army). The clinical manifestations exhibited by all these patients were as follows:

1. Abrupt onset.
2. Temperatures high, in some cases 105° F., lasting from 1 to 5 days, most commonly 3 days.
3. Aches and pains in muscles with severe headache and often pain in the eyes on pressure or movement.
4. Diffusely injected conjunctivae.
5. Low white counts averaging 3,000 with tendency to lymphocytosis.
6. Complete recovery with only symptomatic therapy.

Major Hertig reported that *P. papatasi* was practically the only sandfly found in the building occupied by these people. The sera, which were stored in Dry Ice from the time they were collected, ultimately reached the United States and after a number of months were used for passage in human volunteers at the New Jersey State Prison in Trenton.

The serum of one patient was selected for trial because it was obtained within 24 hours after onset of his fever. It was collected on 12 July 1944, and tested on 18 December 1944; 1 cc. of this serum was injected intracutaneously

in five different sites, and 4.4 cc. were given intravenously to one human volunteer. After an incubation period of 3 days, this volunteer developed a 3-day fever associated with the same type of symptoms which were exhibited by the patients in Naples (that is, those ordinarily found in sandfly fever), and this was associated with a change in the leukocytes also characteristically found in sandfly fever or dengue. Blood was obtained from this volunteer within 24 hours after onset of his symptoms and fever, and *A. aegypti* mosquitoes were allowed to feed on him at that time. The serum from this volunteer was subsequently inoculated, during the course of various experiments, in nine other volunteers and reproduced the same disease. The incubation period was, in all instances, short, usually 3 days, and in no instance was any lesion produced locally at the site of inoculation, nor did rash occur in any of the volunteers. Two volunteers who had recovered from typical attacks following infection with the Sicilian strain of sandfly fever virus 6 weeks and 11 weeks before, respectively, were not immune upon inoculation with this Naples strain of virus. Their disease was in no way different from that of the controls nor from their original attack of sandfly fever. Two other volunteers, who had recovered from typical, proved infections with the Hawaii strain of dengue virus, 6 weeks and 10 weeks before, respectively, developed unmodified attacks of the disease following inoculation with the Naples strain of virus. Large numbers of *A. aegypti* mosquitoes which fed on two human volunteers within 24 hours after onset of their fever were subsequently allowed to bite two other volunteers after prolonged periods of extrinsic incubation. One of the volunteers was bitten by a total of 93 *A. aegypti* mosquitoes (13 after an 18-day extrinsic incubation period, 30 after a 29-day extrinsic incubation period, 24 after a 21-day incubation period, and 26 after a 32-day incubation period). The other volunteer was bitten by a total of 84 mosquitoes (20 within a 13-day extrinsic incubation period, 33 within a 17-day extrinsic incubation period, and 31 within a 24-day extrinsic incubation period). Both of these volunteers remained entirely well and 3 to 4 weeks after this exposure were inoculated with the Naples virus infectious serum. Both developed the typical experimental disease indicating that they were susceptible to this virus and that the *A. aegypti* mosquitoes could not act as a vector of this agent.

Thus, we had evidence of an agent which was capable of reproducing a disease simulating sandfly fever in human beings, incapable of being transmitted by *A. aegypti*, but at the same time immunologically unrelated to both the dengue and the sandfly fever viruses. In order to determine whether or not the lack of immunologic relationship or cross-immunity with sandfly fever virus worked both ways, two volunteers who had recovered from infection with the Naples virus were reinoculated with the same virus 1 month later. They resisted this second inoculation although other volunteers inoculated simultaneously developed the disease in the usual fashion. These two volunteers, thus shown to be resistant to the Naples virus, were then inoculated with

the Sicilian strain of sandfly fever virus and proceeded to develop after the usual incubation period a typical attack of sandfly fever. Accordingly, it was proved that the Naples virus, which was capable of giving rise to immunity to itself, was incapable of producing resistance to the only available type of sandfly fever virus. Conversely, the Sicilian-Middle East type of sandfly fever virus capable of giving rise to immunity to itself was incapable of inducing resistance to the Naples virus. The only way to prove that the Naples virus was indeed a sandfly fever virus would have been to establish the fact of its transmissibility by *P. papatasi*. Since *P. papatasi* could not be imported into the United States, and since it was not feasible to carry out such tests at that time elsewhere, a gradocol membrane filtration test was carried out to determine whether the particle size of this unknown Naples strain would be similar to or different from that of the Sicilian-Middle East type of sandfly fever virus. Since the number of volunteers available for this work at that time was already limited, a small test was carried out. Serum of known infectious potency diluted 1:4 in physiologic salt solution was serially put through gradocol membranes having an average pore diameter of 770, 600, 400, 270, 101, and 75 m $\mu$ . The filtrates from the 400, 270, 101, and 75 m $\mu$  membranes were each injected into one volunteer intravenously in amounts of 10, 11, 16, and 7.5 cc., respectively. The volunteers who received the 400 and 270 m $\mu$  filtrates each developed the typical experimental disease, while those who received the 101 and 75 m $\mu$  filtrates remained well. Accordingly, even in this limited test, it was found that the filtration endpoint of the Naples virus was identical with that previously obtained with the Sicilian strain of sandfly fever virus. Thus, even though it proved impossible to carry out the definitive test of transmission by *P. papatasi*, the available laboratory and circumstantial epidemiologic evidence suggest that the Naples strain of virus in all probability is a strain of sandfly fever virus which is immunologically distinct from the Sicilian-Middle East variety.<sup>51</sup> It has, therefore, been demonstrated for the first time that multiple immunologic types of sandfly fever virus might exist, which could explain the reports of multiple attacks in one season.

Only limited tests with the Naples strain of virus were carried out in laboratory animals. Serum freshly obtained from human volunteers within 24 hours after onset of their fever was inoculated intracerebrally into 2-week-old Swiss mice. Of the 18 mice inoculated with human serum, 4 developed rather definite signs of central nervous system disturbance 5 to 6 days after inoculation, and 3 of these 4 mice died. However, passage of 2 of these mice into 28 others yielded completely negative results. This work had to be discontinued before it could be determined whether or not inapparent multiplication of the Naples virus occurred in the brains of mice.

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<sup>51</sup> Letter, Lt. Col. Albert B. Sabin, MC, to Preventive Medicine Service, Office of The Surgeon General, attn: Brig. Gen. S. Bayne-Jones, 25 Jan. 1945, subject: Isolation of a Sandfly Fever-like Virus, Immunologically Distinct From the Sicilian Sandfly Fever and Hawaiian Dengue Viruses, From the Serum of a Patient With a Febrile Illness Occurring Among Personnel of the AFHQ in Italy During the Summer of 1944.



## CONCLUSIONS

In conclusion, it may be said that while the laboratory investigations on the virus or viruses of sandfly fever, which were encountered in the Mediterranean area and in the Middle East, gave us a good deal more information on the basic properties of the virus and, also, provided a supply for storage and future studies, the primary objectives of developing some method of propagating the virus outside the human body and of a vaccine for the protection of exposed personnel were not attained. It is, therefore, particularly fortunate that DDT was found to be so highly effective for the control of *P. papatasi* in dwellings and that the available mosquito repellents proved so effective in protecting those who may be exposed out of doors. Even if future efforts should not lead to the discovery of a vaccine, sandfly fever need no longer be the military problem that it had been in various operations in endemic areas in the past.

## FIELD OBSERVATIONS ON SANDFLY FEVER IN AMERICAN FORCES WITH SPECIAL REFERENCE TO PERIOD OF COMBAT IN SICILY IN 1943

*Albert B. Sabin, M.D.*

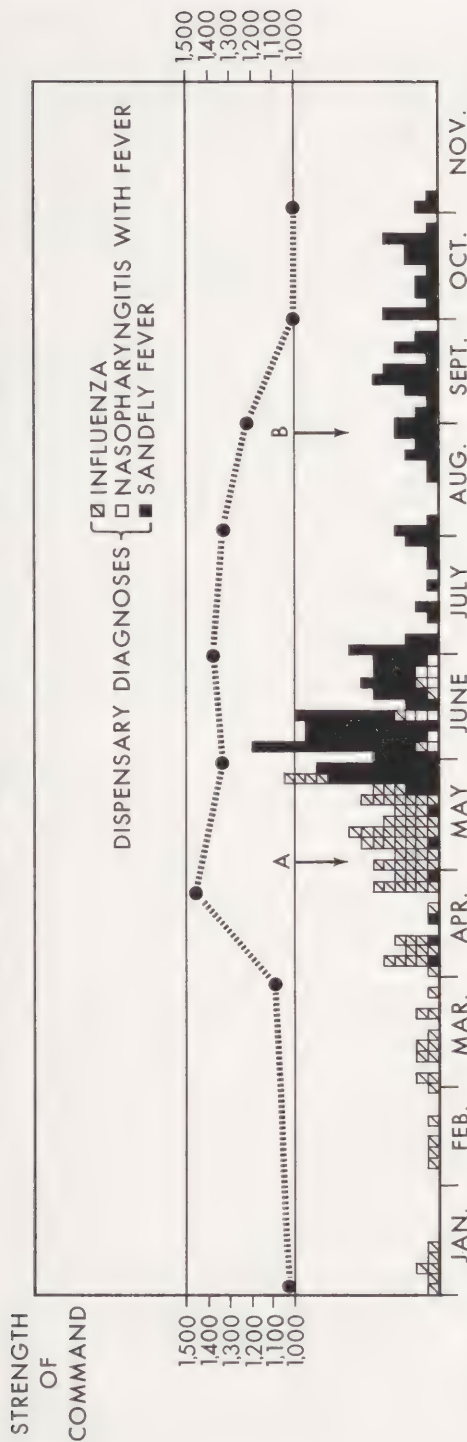
The field observations to be related in this section in the history of sandfly fever during World War II are intended to illustrate the following points:

1. The sources of confusion resulting from unfamiliarity with the disease.
2. The inadequacy of official statistics on this disease.
3. The unfortunate results of treating all F.U.O.'s as potential cases of malaria under the pressure of combat conditions in a region where sandfly fever is endemic.
4. The importance of this disease under combat conditions in Sicily in 1943.
5. The failure of putting to practical use the available information on insect repellents.

### Early Experiences

In June and July 1943, two epidemics of sandfly fever were observed by members of the Commission on Neurotropic Virus Diseases, Army Epidemiological Board, stationed in the Middle East, the first being at Deversoir Field near the Great Bitter Lake on the Suez Canal, and the second at Camp Atterbury in Teheran (Iran) (p. 134). At Deversoir Field, the epidemic was 2 months old before its real nature became apparent to the medical officers attached to the installation. The presence of *P. papatasi* and of an illness compatible with sandfly fever was confirmed by members of the Commission, and Dr. John R. Paul, Director of the Commission, made a personal examination of the dispensary records from January to December of 1943 and graphically summarized the data shown here as chart 10. It is noteworthy that in the beginning sandfly fever was commonly diagnosed as influenza. While the secondary increase in the number of cases during September and October is associated with cessation of isolation of patients, it is not known to what extent newly arrived personnel or an increase in the number of sandflies or a change in climatic conditions may have been involved. Nevertheless, it is known that patients, who are not isolated or otherwise protected from sandflies, may serve to increase the infection rate among sandflies. During the first month of the epidemic in Teheran, the cases were listed and treated as malaria.

CHART 10.—*Epidemic of sandfly fever at Deversoir Field, Suez Canal, 1943*



NOTE.—Arrow at point A indicates date on which "isolation" of cases was begun and at point B on which it was stopped. Each small square represents one case.

### Clinical and Epidemiologic Survey in Sicily

In view of these earlier experiences, it appeared desirable to estimate, if possible, the extent to which sandfly fever was a problem during the period of active military operations in Sicily. The presence of *P. papatasi* and *P. perniciosus* on the island was previously recorded and confirmed in August 1943, by Maj. (later Col.) Cornelius B. Philip, SnC, the entomologist of the Commission on Neurotropic Virus Diseases in the Middle East. The clinical and epidemiologic survey was made by this author during the first week of September 1943, and most of what follows is taken from a report which he submitted to Col. Daniel Franklin, Surgeon, Seventh U.S. Army, at that time and from supplementary data contained in his diary and files.

The extent to which American troops were being affected by sandfly fever was estimated according to two lines of thought: First, by comparison of the clinical manifestations and course of "fevers" observed in evacuation and field hospitals with those of known sandfly fever (the medical officer making this comparison and submitting this report had just spent 4 months in the Middle East observing this disease as it occurs in troops and studying the experimental disease as it was reproduced in American volunteers); second, by determination of the probably relative proportion of malaria and the syndrome corresponding to sandfly fever on the basis of the clinical course and manifestations of a large sample of "fevers" *unaffected by the early administration of the routine course of antimalarial therapy.*

Extensive rounds were made at the 59th and 91st Evacuation Hospitals and at the 11th Field Hospital, where large numbers of patients diagnosed as malaria, F.U.O., and sandfly fever were examined and questioned. The findings were as follows:

**59th Evacuation Hospital.**—Cases then in the hospital diagnosed as pappataci fever had not received the routine course of antimalarial therapy and presented a syndrome entirely compatible with that disease.

Cases of fever were seen in the first and second days of the disease whose symptoms suggested pappataci fever and were not submitted to the course of antimalarial therapy.

The term "F.U.O." in this hospital was reserved for cases with negative malarial smears and clinical histories which suggested to them neither malaria nor pappataci fever, nor any other diagnosis. These were untreated, except for codeine and aspirin, and recovered spontaneously within a few days. My examination of such patients on the wards, as well as of the clinical records of those that had been discharged, led me to the belief that practically all of these patients presented syndromes compatible with the various manifestations of sandfly fever.

As regards malaria, the records of this hospital are confused by the fact that when the hospital first arrived on the island, there had been evacuated to it a large number of patients with the diagnosis of malaria on whom routine antimalarial therapy had already been started. It was believed, however, that many of these patients did not have malaria and that in many instances the reports of positive smears which came with those patients could not be relied upon. Among the patients now on the wards, however, it was striking how the histories of those diagnosed as malaria, whether or not the smear was positive, differed significantly from those diagnosed as pappataci fever or F.U.O.

Because standard criteria were not employed by all the medical officers in this hospital, it was not possible to use the registrar's report for a reliable estimate of the proportion of probable malaria and sandfly fever. Among the patients on the wards, there were at least as many with the diagnoses F.U.O. and pappataci fever as there were with malaria.

**91st Evacuation Hospital.**—This hospital presented, in my opinion, the best opportunity for estimating the relative proportion of sandfly fever and malaria occurring in at least one part of Sicily, for the following reasons:

1. After approximately the first 3 weeks in Palermo (27 July to about 15 August 1943) *routine antimalarial therapy was no longer started immediately on all fevers.* It was not administered until the clinical course, with or without positive smear, suggested malaria



Thus, it was observed that a large number of the fevers defervesced spontaneously and presented a clinical syndrome entirely compatible with sandfly fever.

2. The medical officers had decided to use standard criteria for diagnosis of pappataci fever and malaria. F.U.O. was used only on the wards until the clinical course of the case became clear, and it practically disappeared as a discharge diagnosis from the registrar's records.

3. The registrar's statistics for the period of 14 August to 3 September are based on the criteria just mentioned.

On one ward of 52 patients, there were 16 with typical histories and courses of pappataci fever unaffected by antimalarial therapy and perhaps 4 to 6 more still diagnosed as F.U.O.

At my request, the registrar, Capt. Stewart C. Wagoner, MC, prepared the statistics separately for the first period (27 July to 13 August) and for the second period (14 August to 3 September). These statistics are shown in table 29 and throw the best light on the proportion of probable malaria to probable sandfly fever.

The statistics of the first period are not unlike those of the 59th Evacuation Hospital, while those of the second period present perhaps the most accurate picture of what occurred among a group of 922 cases of "fever" (excluding dysentery and diarrhea). Approximately 69 percent of these (637 cases) could be considered as pappataci fever—their clinical course was compatible with that disease; they recovered promptly without antimalarial therapy, and their malaria smears were negative.

During the second period, the probable sandfly fever cases constituted 58.6 percent (637 of 1,087) of the total communicable diseases and 33.3 percent (637 of 1,914) of all the admissions to the 91st Evacuation Hospital.

**11th Field Hospital.**—The situation in this hospital was still the same as that which prevailed everywhere during the early weeks of the campaign; that is, practically all patients with fever except those with obvious dysentery were put on the routine course of antimalarial therapy.

The medical officers had heard of sandfly fever but did not attempt to make the diagnosis.

TABLE 29.—*Admission, classification, and discharge diagnosis, 91st Evacuation Hospital, Palermo, Sicily, 27 July–3 September 1943*

Classification or discharge diagnosis	27 July– 13 August	14 August– 3 September	Total
	<i>Number</i>	<i>Number</i>	<i>Number</i>
Battle casualties.....	438	53	491
Injuries.....	346	162	508
All diseases.....	2,899	1,699	4,598
Total admissions.....	3,683	1,914	5,597
Dysentery.....	29	56	85
Diarrhea.....	212	109	321
Pappataci fever.....	53	637	690
Fever of undetermined origin.....	305	4	309
Malaria:			
Unclassified (positive smear).....	54	35	89
Unclassified (negative smear, diagnosed clinically).....	790	86	876
Tertian.....	246	95	341
Estivo-autumnal.....	199	65	264
Total communicable diseases.....	1,888	1,087	2,975

NOTE.—After about 14 August 1943, malarial therapy was no longer administered routinely to all "fevers."

Of four new patients with negative malaria smears whom I examined and questioned, three gave rather typical stories for beginning sandfly fever (these would have been observed at the 91st Evacuation Hospital but were immediately started on antimalarial therapy here) and one a similarly suggestive story of malaria—a history of recurrent attacks of fever and spontaneous defervescence over a period of 5 days with a temperature of 98.4° F. on admission.

Two patients who had positive smears and had been receiving the course of antimalarial therapy for a number of days were examined and questioned. One gave a typical history of malaria; that is, recurrent chills and fever before treatment and for a period of 3 days after quinine. The other, however, gave a common story of sandfly fever with a temperature of 101° F. on the first day, 100° on the second day, and 99° on the third day of his illness.

One patient who was said to have a positive smear on admission presented the most characteristic manifestations and course of infectious hepatitis.

The problems presented by some of these patients are (1) the occurrence of other febrile diseases among individuals with positive malaria smears on suppressive therapy, and (2) the number of smears that may erroneously be called positive in the field.

### Estimated Incidence

An estimate of the extent to which the fevers (malaria and pappataci) were a problem during the campaign was obtained from interviews with the commanding officer of the 56th Medical Battalion and the surgeon of the 3d Infantry Division of the Seventh U.S. Army, and from the statistical compilation which was made available by the Office of the Surgeon, Seventh U.S. Army.

From the 56th Medical Battalion, it was learned that, during the first 10 days of the campaign, fevers were not a problem and that casualties constituted the major part of their work. After 22 July, however, the impression was that casualties made up only 10 percent of their work and the fevers most of the remainder. Antimalarial therapy was started on practically all fevers, and because the patients were quickly evacuated, there was no opportunity to reach any final conclusion on the nature of the disease in most instances. The impression was that many of the smears were probably erroneously called positive and that at least a certain number of untreated troops had self-limited, short (2- to 4-day) fevers incapacitating them for 5 to 7 days.

From the 3d Infantry Division, it was also learned that the fevers did not become a problem until after 21 July when the division entered and bivouacked in Palermo. During the second part of their campaign, 1-17 August, with a total strength of 18,814, they had 1,257 cases of disease, 201 of injury, and 1,055 of wounded. Although the division adopted a rigid Atabrine (quinacrine hydrochloride) discipline after 23 July (0.1 gm. being taken daily), the cases of fevers continued to mount. However, very few men were lost to the division as a result of fevers. The majority were evacuated to the field hospital and to the evacuation hospital which followed the division and were returned to duty in 4 to 10 days. The percentage sick in hospital at any one time was not more than 1 percent, and the function of the division was said not to have been affected seriously.

The statistics for disease reported for the entire Seventh U.S. Army during the period of 10 July 1943 (D-day) to 3 September 1943 (table 30) listed only 248 cases of sandfly (pappataci) fever, but at the same time, there were 6,862 cases of F.U.O. and 7,382 cases of malaria, of which only 4,831 had positive smears. The combined incidence of sandfly fever, F.U.O., and malaria was 14,492. If the same proportion (87.6 percent) of sandfly fever which was found among the 922 carefully observed patients with this group of "fevers" at the 91st Evacuation Hospital is applied to the fever cases (9,661, excluding the 4,831 malaria cases reported to have had positive smears) for the entire Seventh U.S. Army, for the reported period, it is estimated that approximately 8,500 may have been

sandfly fever.<sup>52</sup> The admission diagnosis in the majority of these cases was F.U.O. and the proper diagnosis made only on discharge when it was justified by the clinical course of the illness.

TABLE 30.—*Incidence of disease in entire Seventh U.S. Army between 10 July 1943 (D-day) and 3 September 1943*

Classification	Period ending—								Total
	July			August				3 Sep-tember	
	17	24	31	6	14	20	28		
Communicable diseases.....	66	92	230	122	200	179	163	154	1,206
Venereal diseases.....	29	17	49	39	78	89	85	81	467
Dysentery.....	37	84	83	107	169	186	154	139	959
Diarrhea.....	41	331	399	280	386	301	289	247	2,274
Jaundice.....	5	2	4	2	13	10	24	17	77
Sandfly (pappataci) fever.....			1	7	13	85	49	93	248
Fever of undetermined origin.....	94	224	1,117	1,812	1,581	844	657	543	6,862
Malaria.....	81	233	436	844	1,935	1,650	1,246	957	17,382

<sup>1</sup> Total number with positive blood smears 4,831.

Source: Compiled from records in the Office of the Surgeon, Headquarters, Seventh U.S. Army, Palermo, Sicily.

The effect of increased familiarity with the disease and of the cessation of routine antimalarial therapy to all undiagnosed fevers on the relative incidence with which malaria and sandfly fever were diagnosed in one evacuation hospital (91st) in Sicily is shown in table 31. It can be seen that the change in the incidence of sandfly fever from 1.4 percent to 33.3 percent of all admissions is correlated with a drop of F.U.O. from 8.3 percent to 0.2 percent and of "negative-smear-unclassified" malaria from 21.4 percent to 4.5 percent. Birt,<sup>53</sup> in 1915, writing of the British experience in India, suggested that before 1905 most cases of sandfly fever were diagnosed as malaria and made a remark which also appears to be applicable to the American experience in Sicily in 1943:

"\* \* \* Without doubt many of the cures attributed to quinine have been in times past nothing but the natural terminations of cases of sandfly fever. Since five or six thousand attacks of sandfly fever occur annually among the European and Indian troops, the amount of quinine which has been uselessly expended has been enormous."

Of even greater importance than the waste of quinine may have been the needless evacuation of some thousands of men to the communications zone in Africa for further treatment against a malaria which was nonexistent. The extent to which this may have occurred is again suggested by the statistics obtained by the writer from the 91st Evacuation Hospital, which, it is to be recalled, established rigid criteria for the diagnosis of malaria and sandfly fever after about 13 August. Nevertheless, during the period of 27 July to 25 August 1943, this hospital evacuated to the communications zone 2,899 patients. Of these, 382 were battle casualties and 2,517 were patients who had been admitted for disease and nonbattle injury. It is clear from other statistics of this hospital already

<sup>52</sup> From subsequent tabulations of individual medical records, which incorporate corrections in diagnoses, it was shown that a total of approximately 3,600 cases of sandfly fever occurred among U.S. Army personnel in the Mediterranean theater in 1943. About 3,200 of these cases occurred during the 3 months, July–September.

<sup>53</sup> Birt, C.: Phlebotomus Fever (Sandfly Fever); Phlebotomus or Sandfly Fever. Brit. M.J. 2: 168–169, July 1915.



TABLE 31.—*Effect of increased familiarity with the disease and cessation of routine antimalarial therapy to undiagnosed fevers on incidence of diagnosis of sandfly fever, 91st Evacuation Hospital, Palermo, Sicily, 27 July–3 September 1943*

Period	Total admissions (number)	Percent of total admissions diagnosed as—						
		Sandfly	F.U.O.	Malaria				
				Unclassified (negative smear)	Unclassified (positive smear)	Tertian	Falci-parum	All types
27 July–13 August (antimalarial therapy given to all undiagnosed "fevers")-----	3, 683	1.4	8.3	21.4	1.5	6.7	5.4	35.0
14 August–3 September (no antimalarial therapy to undiagnosed "fevers")-----	1, 914	33.3	.2	4.5	1.8	5.0	3.4	14.7

presented in tables 29 and 31 that a large number of these were made up of patients on whom quinine therapy was begun without clearly establishing the diagnosis of malaria.

### Insufficient Use of Insect Repellents

It is important to bear in mind that the events in Sicily in 1943 occurred before the important demonstration by Major Hertig of the great effectiveness of DDT in the control of *P. papatasii*. Nevertheless, it is equally important to recall that the large stores of insect repellent, which had been accumulated by the Army, and whose effectiveness against *P. papatasii* had been demonstrated in May 1943, were practically not utilized at all in the campaign in Sicily, which did not begin until 10 July 1943. Personal inquiry revealed that neither the medical officers nor the command officers were aware of the protective properties of insect repellents against *P. papatasii* and apparently had not been alerted regarding sandfly fever as a possible, significant cause for disease and noneffectiveness in this area of operations. It seemed quite clear to this investigator that the Sicily Campaign failed to benefit from the extensive work that had been done on insect repellents, because the successful use of repellents depends to a large extent on enforcement by command officers, who must be informed and advised by their medical colleagues.

## CHAPTER X

# Typhus Fevers

*Stanhope Bayne-Jones, M.D.*

### Part I. Epidemic (Exanthematic) Louseborne Typhus

The two varieties of typhus fever, epidemic and murine, to be considered in this chapter are a closely related pair among the arthropodborne rickettsial diseases of man. Although they have a number of similar characteristics, they differ to such an extent that they require separate sections for the accounts of their occurrence, effects, and measures for their prevention and control. Accordingly, part I will deal with epidemic (exanthematic) louseborne typhus and part II, with murine (endemic) fleaborne typhus.

From the vantage ground of modern control over these diseases, it is possible to write about them less luridly than has been the custom in the past. Nevertheless, some of their traditional characteristics must be recalled to provide a basis for understanding not only the precautions that were taken routinely, but also the occasional excesses, inspired by terror, that were committed in the cause of protecting troops and civilians against the possible ravages of epidemic typhus. Throughout centuries, epidemic typhus has been dreaded as a killer, a disorganizer of human communities, and a threat to military operations. It has been notorious as one of the great pestilential scourges accompanying war, famine, and the dismal calamities of nations. It has determined the outcome of military campaigns and has had a fateful influence upon the course of history.

During World War II, epidemic typhus was no problem in the continental United States. It occurred in this country only in occasional cases of men brought in by airplane while they were in the incubation period or early stages of the disease. The mild form of recrudescent typhus known as Brill's disease was of no military consequence. On the other hand, epidemic typhus was a constant threat in most of the theaters of operations overseas, except in the Middle, South, and Southwest Pacific Areas. In North Africa, the Middle East (Near East), Europe, Japan, and Korea, it occurred in severe epidemics among the civilian populations and occasionally in small episodes among U.S. Army personnel. In contrast, murine typhus was a problem for American troops in camps, in extracantonment areas, and in the regions used for maneuvers in the southern portions of the United States, and to a slight extent in Hawaii.

## GEOGRAPHIC DISTRIBUTION OF EPIDEMIC AND MURINE TYPHUS

The occurrence and degree of incidence of epidemic and murine typhus in various parts of the world are indicated in map 3. This map is essentially the same as the one prepared in the Preventive Medicine Service, Office of The Surgeon General, in 1943. The chief additions are the heavy shading over Japan to indicate the high incidence of epidemic typhus there in 1945, and the cross hatching over northeastern United States and Yugoslavia to indicate the occurrence of Brill's disease, definitely recognized since 1951 as recrudescence epidemic typhus.

## THE RICKETTSIAL DISEASES OF MAN

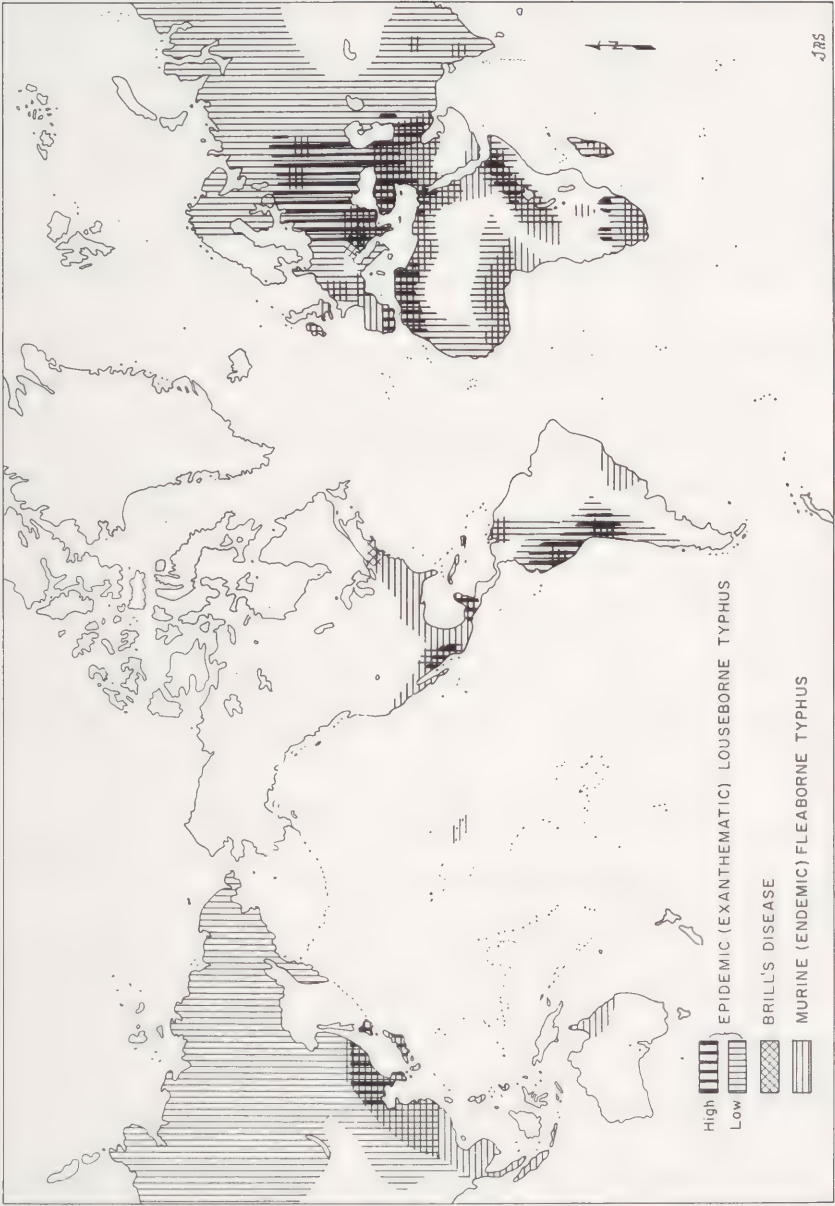
The rickettsial diseases of man, which include the typhus fevers, are caused by minute, highly parasitic micro-organisms occupying a biologic position between the bacteria and the viruses. The organisms usually occur within the endothelial cells of the smaller blood vessels of many organs of the body, and circulate in the bloodstream in the early phases of infection. They have not been cultivated outside of living animal cells. Nearly all species are transmitted by arthropods, but some can be transmitted aeriaily by particles which are inhaled, or are deposited in the conjunctival sac of the eye or upon the mucous membrane of the nose of the human victim. Some have reservoirs in the lower animals, such as rats, mice, voles, rabbits, and dogs. Their cycles of growth are complicated and are not fully known for all species. As the etiological agents of the more important rickettsial diseases of man, such as the typhus fevers, have stages in arthropods, these agents are particularly vulnerable to attack directed against their insect vectors. Hence, during World War II, control measures were based largely upon destruction of the insect transmitters. In addition, a considerable degree of protection was gained by immunization with vaccine composed of rickettsial bodies and their antigenic components. During the war, the treatment of typhus was supportive, although some progress in chemotherapy was made by the administration of PABA (para-aminobenzoic acid). Effective therapy with antibiotics (chloramphenicol, Aueromycin, and terramycin) was not developed until 1948 and later. For an authoritative presentation of information about the rickettsial diseases of man, the reader is referred to the treatise edited by Rivers.<sup>1</sup>

During World War II, the important groups of the rickettsial diseases of man from the point of view of military preventive medicine were the typhus

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<sup>1</sup> Rivers, Thomas M. (editor): *Viral Infections of Man*. Philadelphia: J. B. Lippincott Co., 2d edition, 1952. In this volume see especially: Snyder, J. C.: The Typhus Fevers, pp. 578-610; Cox, H. R.: The Spotted Fever Group, pp. 611-637; Smadel, J. E.: Scrub Typhus, pp. 638-651; and Smadel, J. E.: Q Fever, pp. 652-664.





MAP 3.—Outline map of the world showing the approximate geographic distribution of epidemic (exanthematic) louseborne typhus, murine (endemic) fleaborne typhus, and Brill's disease.

fevers,<sup>2</sup> the spotted fevers (ch. XII), scrub typhus (ch. XI), and Q fever.<sup>3</sup> Trench fever, which caused so much illness among American and British troops during World War I, did not reappear during World War II. The reason for this is as unclear as are the uncertainties as to the true nature of the disease called trench fever. Rickettsial pox was not discovered until after the war, and there are no retrospective diagnoses of it among troops of the war period.

Statistics of the incidence of the chief rickettsial diseases and the deaths they caused among U.S. Army personnel from 1942 through 1945 are presented in table 32. These figures were compiled from medical records giving final diagnoses.

The statistics in table 32 epitomize an experience that was not expected when the United States entered the war. Among troops, the dreaded epidemic

TABLE 32.—*Incidence of and deaths due to certain rickettsial diseases in U.S. Army personnel during World War II, 1942-45*

[Preliminary data based on sample tabulations of individual medical records]  
[Rate expressed as number of cases per annum per 1,000 average strength]

Rickettsial disease	Number of cases	Incidence rate	Number of deaths
Epidemic (exanthematic) louseborne typhus:			
Continental United States-----	0	0	0
Overseas-----	104	. 01	0
Total Army-----	104	0. 00	0
Murine (endemic) fleaborne typhus:			
Continental United States-----	497	. 03	1
Overseas-----	290	. 03	14
Total Army-----	787	. 03	15
Scrub typhus, miteborne, tsutsugamushi disease:			
Continental United States-----	5	0. 00	1
Overseas-----	5, 436	. 52	282
Total Army-----	5, 441	. 21	283
Undifferentiated typhus-----	110	0. 00	0

NOTE.—Absolute zero is indicated by zero in the units column; 0.00 indicates a rate of more than zero but less than 0.005.

<sup>2</sup> For a detailed presentation of the clinical and immunological aspects of typhus fevers, see Zarafonitis, Chris J. D.: *The Typhus Fevers*. In *Medical Department, United States Army. Internal Medicine in World War II. Volume II. Infectious Diseases*. Washington: U.S. Government Printing Office, 1963, pp. 143-223.

<sup>3</sup> Dingle, John R.: *Q Fever*. In *Medical Department, United States Army. Preventive Medicine in World War II. Volume V. Communicable Diseases Transmitted Through Contact or By Unknown Means*. Washington: U.S. Government Printing Office, 1960, pp. 401-410.

typhus with only 104 cases and no deaths was much less a cause of sickness and loss of life than was the more complacently regarded murine typhus, which caused 787 cases and 15 deaths. The low incidence and absence of mortality of epidemic typhus attest to the extraordinarily effective measures that were applied for the protection of troops in all areas in which that disease was occurring, sometimes in epidemic proportions, among the enveloping civilian populations. On the other hand, there was a mistaken notion that murine typhus was a mild disease only. Control measures against it were less complete and less effective, and troops were not vaccinated against murine typhus. In another direction, the violence of the onslaught of miteborne scrub typhus in the Southwest Pacific Area (chiefly in New Guinea and adjacent islands, and in the Philippines) and in the China-Burma-India theater had not been anticipated. At the start, little information was available upon which to base estimates of the risks from scrub typhus in those areas. Protective measures had to be devised in the midst of the encounter. There was no specific therapy. During the period from 1942 through 1945, scrub typhus was the cause of illness in 5,441 military personnel, with 283 deaths. It was the most serious of the rickettsial diseases that affected U.S. Army personnel. Scrub typhus, however, unlike epidemic typhus, lacked the potentiality of causing widely spreading epidemics because it was not transmissible from person to person. In several instances, nevertheless, it was a serious hindrance to military operations.

The incidence of epidemic, louseborne, typhus fever in the U.S. Army by theater and year, 1942-45, is shown in table 33. There were no deaths from epidemic typhus among troops. The average duration of illness was 22 days. The estimate of daily noneffectiveness per 1,000 average strength was less than 0.005—a negligible rate.

## EPIDEMIC (LOUSEBORNE) TYPHUS

### Historical Review to 1941

By exerting great influence upon the undertaking and outcome of military campaigns and by killing thousands to millions of people or by so sickening populations as to keep them depressed for long periods, epidemic typhus has been at times a major determinant of political, economic, and military conditions. While this has occurred in many countries, the most important in recent times were the outbreaks of typhus in Europe, the Balkans, Russia, North Africa, and the Middle East. The volumes of Prinzing<sup>4</sup> and Zinsser<sup>5</sup> are still standard sources of information on these subjects. So much has been written about these outbreaks of typhus that it is not necessary to review them in detail here.

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<sup>4</sup> Prinzing, Friedrich: *Epidemics Resulting From Wars*. Oxford: Clarendon Press, 1916.

<sup>5</sup> Zinsser, Hans: *Rats, Lice, and History*. Boston: Little, Brown, and Co., 1935.



TABLE 33.—*Incidence of epidemic (exanthematic) louseborne typhus fever in the U.S. Army, by theater or area and year, 1942-45*<sup>1</sup>

[Preliminary data based on sample tabulations of individual medical records]  
 [Rate expressed as number per annum per 1,000 average strength]

Theater or area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States.....	0		0		0		0		0	
Overseas:										
Europe.....	10	0.00	0		0		0		10	0.00
Mediterranean <sup>2</sup> .....	16	.01	1	.04	12	.03	3	0.00		0
Middle East.....	14	.11	1	.17	8	.15	0		5	.18
China-Burma-India.....	63	.14	1	.11	25	.63	12	.07	25	.11
Southwest Pacific.....	0		0		0		0		0	
Central and South Pacific.....	1	0.00	0		1	0.00	0		0	
North America <sup>3</sup> .....	0		0		0		0		0	
Latin America.....	0		0		0		0		0	
Total overseas.....	104	0.01	3	0.01	46	0.03	15	0.00	40	0.01
Total Army.....	104	0.01	3	0.00	46	0.01	15	0.00	40	0.01

<sup>1</sup> Revised to include changes made up to 5 Oct. 1960.

<sup>2</sup> Includes North Africa.

<sup>3</sup> Includes Alaska and Iceland.

NOTE.—Absolute zero is indicated by zero in the units column; 0.00 indicates a rate of more than zero but less than 0.005.

Naples, Italy, has been a point of concentration in the scientific, political, and military peregrinations of epidemic typhus. As Zinsser has expressed it, typhus, first definitely described by Fracastorius<sup>6</sup> in 1546 on the basis of earlier observations, “made its political debut—by one of the most far-reaching and profoundly effective strokes of its entire career, playing the decisive role in the relief of the Imperial Army [of Charles V] at Naples when besieged by the French under Lautrec in 1528.” In World War II, the outbreak of typhus in Naples, in 1943-44, was reminiscent of its occurrence at the siege of Naples in 1528. In both instances, typhus had not occurred in Italy during a previous generation and was introduced from the East. Unlike the events of 1528, however, when some 20,000 soldiers and untold numbers of civilians died of the disease, in 1943-44 the potentially dangerous outbreak among the civilian population was quickly brought under control, the disease was prevented from spreading beyond Naples and its vicinity, and there were only a few cases and no deaths from typhus among soldiers of the U.S. Army.

During the early 16th century and for the next 300 years, typhus was constantly prevalent in Europe and took great toll in all of the main military campaigns. During the Thirty Years' War, from 1618 to 1648, typhus oc-

<sup>6</sup> Fracastorius, H.: *De Contagione et Contagiosis Morbis et Eorum Curatione*, Libri III (1546). Translated by W. C. Wright. New York: G. P. Putman's Sons, 1930. See especially: Book I, Contagion, Chapters I-XIII, pp. 3-69; and Book II, Contagious Diseases, Chapter VI, pp. 101-103, The Fever Called Lenticulae or Puncticulae or Peticulae.

curred in almost every country in continental Europe, and in 1700 it spread to England and Ireland. After 1800, a change appeared; thereafter, the outbreaks of typhus among troops and the tremendous epidemics among the civilians occurred mostly in Eastern Europe and Russia. For example, there were severe outbreaks among Napoleon's Army in Russia in 1812, in the Russian, French, and English troops in the Crimean War (1854-56), and in the Russo-Turkish War in 1877. In contrast, there was little or no typhus in the armies in the American Civil War (1861-65) or in the Franco-Prussian War.

From 1600 onward, epidemic typhus was prevalent in North Africa, Egypt, and the Middle East. Outbreaks, from severe to moderate, occurred in Mexico, South America, China, and other areas. Thus, epidemic typhus took up a global position in advance of the global wars and, at an early date, fixed some of the determinants of the preventive medicine program of World War II.

From 1900 to the beginning of World War I in July 1914, typhus continued to occur in a relatively mild manner in most of the countries of Europe and in Russia. However, within 5 months of the beginning of this war, typhus broke out in the Serbian Army and among the thousands of Austrian prisoners of war. It spread with violence through the troops and the civilians and finally enveloped the entire Eastern front. It had a definite influence upon the whole military campaign—directly upon the Eastern, indirectly upon the Western, as it did not occur in France. As Zinsser has said: "Typhus may not have won the war—but it certainly helped."

During World War I (1914-19) and in the succeeding years, typhus achieved its historical ascendancy in Russia alone. It has been estimated that from 1917 to 1922 there were at least 25 million cases of typhus with 2½ million deaths in territories now controlled by Soviet Russia.

A decline of incidence of typhus throughout all the regions of Europe occurred during the 10-year period from 1923 to 1933. Thereafter, there was a notable increase of typhus in many countries, particularly in Rumania, Poland, Yugoslavia, Spain, Egypt, and the Soviet Union, with epidemics impinging upon military operations and civilian movements to 1939-40. At the beginning of World War II, the situation became obscured because of the breakdown of the system of international reporting of infectious diseases. After the war, the assembly of statistics of typhus incidence in the Mediterranean<sup>1</sup> area gave a retrospective view of the high incidence and proportionately great risks, not fully appreciated at the time of the landing in North Africa, to which United States and British troops were exposed in French North Africa, Egypt, and Iran.

Although epidemic typhus fever has probably never been a serious problem, though by no means a negligible one, for the U.S. Army, it is fitting in concluding this historical review to summarize notes from official reports covering the period from 1916 to 1941. It is to be noted that as murine typhus

<sup>1</sup> Bayne-Jones, Stanhope: Epidemic Typhus in the Mediterranean Area During World War II. In *Rickettsial Diseases of Man*. Washington: American Association for the Advancement of Science, 1948, pp. 1-15.

was not differentiated until 1926 and was not included as an item of diagnosis in the Army medical statistics until 1940, the single figures include both types. Probably all but a few cases reported were of the endemic or murine variety. The incidence of typhus fever in the Army during the World War (World War I, 1917-18) was as follows: <sup>8</sup> "United States, 15; Europe, 7; other countries, 19; officers, 1; total 42. To the 42 original admissions for typhus fever must be added 5 more cases in which this malady appeared as a concurrent disease. Three of these individuals died." Most of the Annual Reports of The Surgeons General of the Army for the fiscal years from 1916 to 1941 do not contain any mention of typhus. No definite, unquestionable cases of epidemic typhus appear to have occurred in U.S. troops in the Military Expedition into Northern Mexico (1916), in World War I (1917-18), in the American Forces in Germany (1919-22), in the American Expeditionary Force, North Russia (1918-19), and in the Expeditionary Forces to Siberia (1918-20). At times, as during the latter part of World War I, "up to the signing of the armistice, our armies like those of our allies, were heavily infested with lice, and to such a degree that the condition was alarming." It was reported that over 90 percent of the troops were "in a verminous condition." Alarm was increased when troops came into contact with civilians in typhus-infected areas. Apparently no typhus occurred among military personnel. This was remarkable.

### Scientific Review, 1909-41

In 1909 and 1910, Howard Taylor Ricketts discovered the etiological agent of epidemic typhus. Later, in honor of Ricketts and Stanislas Josef Mathias von Prowazek, both of whom died of the disease while they were working on it, the micro-organism was named *Rickettsia prowazeki*.

Between 1931 and 1938, Zinsser and Castenada, Nigg and Landsteiner, Zia, and Dyer and Bengtson succeeded in growing typhus rickettsiae in various kinds of tissue cultures, but with only meager yields. In 1938, Cox obtained large yields of the *Rickettsia* of Rocky Mountain spotted fever in cultures in the yolk sac membrane of the embryonated hen's eggs, and, in 1940, Cox and Bell had the same success with similar cultures of *R. prowazeki*. This opened the way for new biological discoveries and made possible the production of an effective typhus vaccine and the development of specific diagnostic procedures.

From 1916 until 1941, the diagnostic serology of the typhus group of diseases was based upon the agglutination reactions with suspensions of special strains of *Proteus vulgaris* (OX-19, OX-2, and OX-K). This reaction, described first by A. Felix in 1916 and further elaborated by E. Weil and Felix in 1920, became known as the Weil-Felix reaction. As the bacterial component has no causal relationship to typhus fever, the reaction is a nonspecific one, apparently depending upon a common antigenic fraction shared by both the

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<sup>8</sup> Tasker, Arthur N.: Infectious Jaundice; Typhus Fever; Trench Fever. In The Medical Department of the United States Army in the World War. Washington: U.S. Government Printing Office, 1928, vol. IX, pp. 483-485.



rickettsial organisms and the *Proteus* bacteria. For a while, it was thought that agglutination of OX-19 was diagnostic of epidemic typhus, OX-2 of murine typhus, and OX-K of scrub typhus. Although this was not strictly true, the Weil-Felix reaction, in spite of lack of specificity, was a convenient and useful serological test for making presumptive diagnoses, for following the course of immunization, and for carrying out gross epidemiological surveys. It was used extensively in U.S. Army hospitals and laboratories during World War II until it was supplanted by specific preparations made from rickettsiae obtained in abundance from Cox-type yolk sac cultures. Rickettsial suspensions and antigenic fractions were introduced for use in agglutination and complement fixation tests in 1940-41.

From about 1876, the body louse had been suspected of playing an important role in the transmission of epidemic typhus, but in the absence of proof, many curious and inaccurate notions prevailed. In 1909, Charles Nicolle proved that typhus could be transmitted from man to man by the body louse *Pediculus humanus* var. *corporis*. Nicolle's discovery redirected the attack against the louse vector, and the adjective "louseborne" was added to the name of epidemic typhus. Now, as Zinsser<sup>9</sup> wrote: "The strategic initiative passed into the hands of man \* \* \* the victim was in a position to organize a rationally planned and strategically sound defense against his historic enemy." It was clearly shown in Serbia in 1915,<sup>10</sup> and in Poland in 1920,<sup>11</sup> that, in the absence of lice, typhus is not transmitted from person to person. The all-important mode of transmission is by infected louse feces deposited on the skin while the louse is feeding. Occasionally, infection is produced via the conjunctival sac or upper respiratory tract by dust containing infected louse feces. The survival of *R. prowazeki* in dried louse feces over months may account for the persistence of the micro-organism during an interepidemic season of the year.

The attack upon the louse vector of typhus fever was clumsy and inefficient until after the outbreak of World War II, although studies of possible improvements were underway in the late 1930's. The methods of delousing consisted of heat disinfestation of clothing and bedding, and of bathing and shaving of hair. The U.S. Army entered World War II with the antilouse weapons of World War I—heavy bathing units and steam autoclaves. These methods removed and killed lice, but as they had no persistent or residual action, they left the person vulnerable to reinfestation. Late in the 1920's, and again in about 1941, attention was directed to chemical insecticides as possibly better agents for the control of lice. In 1941, the only available materials known to possess lousicidal properties without being too toxic for man were rotenone and pyrethrum. In the United States in 1941, interest became centered in a prep-

<sup>9</sup> See footnote 5, p. 179.

<sup>10</sup> Strong, Richard P., Shattuck, George C., Sellards, A. W., Zinsser, Hans, and Hopkins, J. Gardner: Typhus Fever With Particular Reference to the Serbian Epidemic. Cambridge, Mass.: American Red Cross, Harvard University Press, 1920.

<sup>11</sup> Wolbach, S. Burt, Todd, John L., and Palfrey, Francis W.: The Etiology and Pathology of Typhus, Being the Main Report of the Typhus Research Commission of the League of Red Cross Societies to Poland. Cambridge, Mass.: League of Red Cross Societies, Harvard University Press, 1922.

aration known as MYL, a louse powder consisting of pyrethrins as the toxicant, mixed with a synergist, an ovicide, an antioxidant, and a pyrophyllite powder as a diluent. MYL was adopted for use by the Army in 1942. DDT was not known to the Army until a year later.

Precision in the knowledge of typhus fevers was greatly sharpened in 1926 by the differentiation of murine, fleaborne, endemic typhus fever from the classical epidemic, louseborne, variety. Zinsser's earlier opinion, later substantiated, that Brill's disease was a form of recrudescent epidemic typhus increased the clarification. These distinctions were of basic importance for the development of programs of prevention and control of epidemic and murine typhus.

### General Measures of Typhus Control

During the period from 1909 to 1941, the following general measures came to be recognized: Case finding, isolation of cases, regional isolation and control, and actions based upon epidemiological intelligence. Combining specific and general elements, a Committee of Experts at a conference held under the auspices of the League of Nations at Geneva, Switzerland, on 8-10 February 1937, summarized a comprehensive program for the control of epidemic typhus as follows:

1. Case finding; "depistage."
2. Isolation of cases; "isolement des malades."
3. Isolation of districts and regions; "cordon sanitaire."
4. Delousing; "epouillage."
  - a. In military groups.
  - b. In civilian groups, including refugees and floating populations.
5. Immunization of individuals and groups (particularly key medical, sanitary, and auxiliary personnel).
  - a. Vaccination against typhus.
  - b. Seroprophylaxis (occasionally) by injections of immune or convalescent sera.

From the foregoing, it is clear that arrays of knowledge of typhus and its control were in existence well before the entry of the United States into World War II. But these principles and procedures had not been marshaled for the purposes of military preventive medicine and the public health programs of civil affairs and military government in occupied and liberated countries in the homelands of typhus. Under the guidance and inspiration of Col. (later Brig. Gen.) James S. Simmons, MC, Chief, Preventive Medicine Service, this knowledge was assembled, applied, and advanced through research. After 1941, the prevention and control of typhus became a worldwide activity of the Preventive Medicine Service and an areawide activity of many medical and line organizations in the continental United States and overseas. Through continuous research and through the development of new potent materials and methods during World War II, control measures gained the capacity to conquer both epidemic and murine typhus.

## PREPARATION DURING THE PRELUDE, 1936-41

On 8 September 1939, shortly after the Nazis invaded Poland and England and France had declared war upon Germany, President Franklin Delano Roosevelt issued his "Proclamation of Limited National Emergency," thereby putting preparedness into motion. The consequences were great for military preventive medicine in general and for the control of epidemic typhus as a specific activity. The Army's wartime program of preventive medicine actually began in 1939, about 2 years prior to America's entry into the war. It was then that The Surgeon General began to revise his plans for the expansion of the entire Medical Department as a part of the Army's preparation for a defensive war.

Under the direction of Maj. Gen. James C. Magee, The Surgeon General (1939-43), the "Surgeon General's Mobilization Plan, 1939" was issued in December 1939. This provided for future enlargement of the unit for preventive medicine, and it was on the basis of this plan that Colonel Simmons was assigned to the Office, to become, after a few months (May 1940), Director of the Preventive Medicine Subdivision in the Professional Service Division, Office of The Surgeon General. Reporting for duty on 24 February 1940, he began at once to initiate developments which became highly important for both military preventive medicine and civilian public health. From the start, he included typhus fevers and other rickettsial diseases among the hazards against which intensified research and the development of new and better methods of prevention and control should be prosecuted vigorously.

Many jurisdictional matters had to be settled through sustained argument. It was not generally understood in military-medical circles that the scope of preventive medicine encompassed the total Army and was not limited to the care of the sick and wounded which many regarded as the main function of the Medical Department. These different roles gave rise to different needs, to conflicts of opinion, and to different systems of administration—all of which had to be reconciled within the professional Medical Department.

During the prelude, as well as throughout the war, there were frequent changes of policy, organization, authority, and commanding personnel from the levels of the General Staff through all intermediate units to small components both at home and abroad. Of special significance for the Medical Department and the Office of The Surgeon General were the establishment and operations of the Services of Supply, later named the Army Service Forces (p. 193). In many of the ensuing situations, the Preventive Medicine Service had to strive to preserve its integrity and secure recognition of what it needed to perform services that were indispensable to the health of the Army.

Appointments of officers in 1940-41 who became chiefs of subdivisions or branches in the Preventive Medicine Service brought into the office able men who took important parts in the future work on typhus. Among these were (listing their final ranks) Col. William S. Stone, MC (Sanitation), Col. Karl R. Lundeberg, MC (Epidemiology), Col. Arthur P. Long, MC (Infectious Dis-



eases), Col. Elliott S. Robinson, MC (Laboratories), Col. Tom F. Whayne, MC (Medical Intelligence), and Col. William A. Hardenbergh, SnC (Sanitary Engineering).

At the end of 1940 and early in 1941, in response to ideas and recommendations of Colonel Simmons, the civilian Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army<sup>12</sup> was established in the Office of The Surgeon General and attached to the Preventive Medicine Service. Later, this organization became known as the Army Epidemiological Board and gained status as a "miscellaneous activity" of the War Department. Originally, it consisted of a central board and 10 commissions composed of 7 to 15 distinguished scientists from the field of investigations of communicable diseases. Although it had a commission for certain viral diseases, there was none specifically designated for typhus or rickettsial diseases. Nevertheless, certain members of the Board and Commissions had expert knowledge and interests in these diseases and contributed to the development of policies and procedures for the control of typhus. Among those to be mentioned especially were Dr. Francis G. Blake, president of the Board, and Dr. Kenneth F. Maxey who, in addition to their other services, took leading parts in the investigation of scrub typhus in New Guinea in 1943.

Extensive and close liaison relationships were established during 1940-41 with many organizations in the field of preventive medicine. These included the Bureau of Medicine and Surgery, U.S. Navy; the American Medical Association; the Pan American Sanitary Bureau; the International Health Division of the Rockefeller Foundation; the Bureau of Entomology and Plant Quarantine of the U.S. Department of Agriculture; the National Research Council; the Committee on Medical Research, Office of Scientific Research and Development; the U.S. Public Health Service; the State Department; the public health organizations of various friendly governments; and other governmental and civilian health organizations.

The cooperation of the U.S. Public Health Service with the Army, which had been notably valuable during World War I, was reestablished in January and February, 1940, through correspondence between the Secretary of War and the Federal Security Administrator, at the instigation of The Surgeon General. The agreement provided that the U.S. Public Health Service, operating under the authority of existing laws and using its own resources, would cooperate with the Army in safeguarding the health of military personnel by suitable measures for extracantonment area sanitation. This arrangement became one of primary importance for the prevention and control

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<sup>12</sup> (1) Memorandum, Lt. Col. James S. Simmons, MC, for the Chief of the Planning and Training Division (through the Chief of the Professional Service Division), 27 Dec. 1940, subject: Establishment of a Board for the Investigation of Influenza and Other Epidemics in the Army [with attached letter for signature of The Surgeon General]. (2) Letter, Maj. Gen. James C. Magee, The Surgeon General, to the Adjutant General, 27 Dec. 1940, subject: Establishment of a Board for the Investigation of Influenza and Other Epidemic Diseases in the Army, with 1st Ind. AG 710 (12-27-40) M-A, War Department, A.G.O., 11 Jan. 1941, by order of the Secretary of War. (3) Bayne-Jones, Stanhope: Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army. Army M. Bull. No. 64: 1-22, October 1942.

of murine typhus among military personnel in contact with rat-infested areas of cities and towns near camps in the South in this country. For the future work on epidemic typhus, it was even more important, going far beyond the normal function of the Service in exercising control over the manufacture of typhus vaccine. Through this relationship, the great laboratories of the U.S. Public Health Service, renowned for studies of rickettsial infections (especially typhus), were brought into close touch with the Army, and the expert services of distinguished and influential men in this field became available for the advancement of the military typhus control program. Especially to be recalled in this connection are Dr. Thomas Parran, Surgeon General, U.S. Public Health Service; Dr. Rolla E. Dyer, Director, National Institute of Health; and Dr. Norman H. Topping, Assistant Chief, Division of Infectious Diseases, National Institute of Health. These three became members of the United States of America Typhus Commission.

An important relationship was established early between the Preventive Medicine Service and the Bureau of Entomology and Plant Quarantine, U.S. Department of Agriculture. As Dr. E. F. Knippling, chief of that Bureau, has written:<sup>13</sup> “\* \* \* in 1941, representatives of the Office of The Surgeon General, U.S. Army, and other responsible medical men among civilian institutions requested the Bureau of Entomology and Plant Quarantine to formulate plans for conducting research on the control of lice, as well as other medically important insects and arachnids.” Colonel Simmons and Major Stone were chiefly instrumental in drawing this Bureau into work on problems of medical military significance. The effective louse powders used by the Army during the war came largely from this collaboration.

Two events that occurred outside the Medical Department during this period of the prelude exerted influence upon preventive medicine and typhus control. The first was the Army maneuvers in the South; the second was the “destroyer deal.”

The large maneuvers conducted by the Army in the South in 1940 and 1941 were the first genuine corps and army maneuvers in the history of the Nation. Large problems of control of insect vectors of disease were encountered, and there was some exposure to murine typhus.

On 3 September 1940, President Roosevelt announced to the Congress that an agreement had been made between the British and United States Governments by which 50 overage destroyers would be exchanged for British naval bases and airbases in Newfoundland, Bermuda, the Bahamas, Jamaica, Saint Lucia, Trinidad, Antigua, and British Guiana. Although the operations of establishment and maintenance of these bases, including the provision of medical services, were primarily under the Corps of Engineers, the Preventive Medicine Service became concerned with the sanitary surveys of the areas, and in the control of malaria and other communicable diseases. For this work, Col.

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<sup>13</sup> Knippling, E. F.: DDT and Other Insecticides for the Control of Lice and Fleas Attacking Man. In *Rickettsial Diseases of Man*. Washington: American Association for the Advancement of Science, 1948, pp. 215-223.

(later Brig. Gen.) Leon A. Fox, MC, was detailed to the Corps of Engineers to direct the medical and sanitary work. Later, after he returned to the Medical Department in 1943, he was promoted to the rank of brigadier general and served as the second Director and first Field Director of the U.S.A. Typhus Commission.

In December 1941, endemic, murine, typhus was found to be fairly prevalent in Jamaica.<sup>14</sup> Through the investigation of the disease by a group sent from the Virus and Rickettsial Diseases Laboratory of the Army Medical School, Washington, D.C., interest in typhus was quickened. Later, the five members of this group, including Lt. Col. (later Col.) Harry Plotz, MC, became attached in various capacities to the U.S.A. Typhus Commission and worked both abroad and in laboratories in this country on problems of epidemic typhus, murine typhus, and scrub typhus.

### FROM PEARL HARBOR TO NORTH AFRICA, 1941-42

This period began with the Japanese attack on Pearl Harbor on 7 December 1941, and the declaration of war on Japan by the United States on the following day. On 11 December, Germany and Italy declared war on the United States, and the United States declared war on those countries. The year included several months of planning and preparation for Operation TORCH, which culminated in the landings of the Allied Forces of the United States and Great Britain in French North Africa on 8 November 1942. Partly as a consequence of this first movement of troops into a typhus-infected region, the United States of America Typhus Commission was established by an Executive order of the President, on 24 December 1942.

**Immunization against typhus.**—Vaccination against epidemic typhus was adopted for the Army on 6 January 1942. As the history of typhus vaccine and a discussion of its use have been presented by Long,<sup>15</sup> in another volume of this series, only a brief abstract with a few additional details will be recorded here.

The first type of typhus vaccine adopted for use in the Army, as recommended by the Division of Medical Sciences of the National Research Council on 22 October 1941, was the Cox vaccine. This consisted of a suspension of typhus rickettsiae (Breinl strain) that had been grown in the yolk sac of embryonated hen's eggs, extracted by centrifugation, washed, and killed with formalin. Its use was prescribed first in War Department Circular No. 4, dated 6 January 1942, which specified in section III: "All military personnel stationed in or traveling through Asia, Africa, continental Europe, or other areas where danger from epidemic typhus exists will be immunized with typhus vaccine as prescribed by The Surgeon General." This War Department cir-

<sup>14</sup> Plotz, H., Woodward, T. E., Philip, C. B., Bennett, B. L., and Evans, K. L.: Endemic Typhus Fever in Jamaica, B.W.I. *Am. J. Pub. Health* 33: 812-814, July 1943.

<sup>15</sup> Long, Arthur P.: The Army Immunization Program. In Medical Department, United States Army. Preventive Medicine in World War II. Volume III. Personal Health Measures and Immunization. Washington: U.S. Government Printing Office, 1955, pp. 271-272 and pp. 319-323.



cular, prepared in the Preventive Medicine Service, stated at this early date a policy that prevailed throughout the war. "Other areas" were specified from time to time, and the composition and dosage schedules of the vaccine were changed as experience dictated.

Early in 1942, it was realized that the original Cox-type vaccine lacked immunizing potency. The antigenic content was thereafter increased by using Craigie's method<sup>16</sup> of ether-extraction of suspensions of rickettsiae from yolk sac cultures and by the addition of a previously discarded soluble specific polysaccharide antigen. This soluble specific substance was discovered almost simultaneously in the first quarter of 1942 by Colonel Plotz<sup>17</sup> at the Army Medical School and by Topping and Shear<sup>18</sup> at the National Institute of Health. Procurement of this improved vaccine took time, and in the meantime, the original type was used. The new type was gradually introduced and was the only type used after March 1943.

The effectiveness of vaccination against typhus was open to question. Results of animal tests became increasingly more favorable with vaccine enriched in antigenic content. That injections of the vaccine into investigators and technicians handling materials containing live rickettsiae protected against fatality, if not against infection, became clear. But evidence from field trials was needed as a basis for making an estimate of the degree of protection that might be expected to exist among vaccinated troops exposed to natural infection from contact with native populations under epidemic conditions during campaigns. Controlled studies of the efficacy of typhus vaccine were made one of the primary objectives of the U.S.A. Typhus Commission, and such studies were carried out in Egypt. The question was answered affirmatively in 1944.

**Control of lice by insecticides.**—In the attack on lice, particularly *P. humanus* var. *corporis*, the transmitter of epidemic typhus, gains were made early in 1942. By the end of the year, the achievement was becoming one of the major scientific advances of the war. Under the direction of Colonel Simmons, Maj. (later Lt. Col.) William S. Stone, MC, Chief of the Sanitation Branch, was the immediate leader of this project in the Preventive Medicine Division. To his foresight and energy is due a large part of the Army's successful control of epidemic typhus. The Sanitary Engineering Branch, Preventive Medicine Division, under Col. William A. Hardenbergh, SnC, also collaborated in the studies on lousicides and carried on extensive work on rodent control. The major collaborating civilian agencies and nonmilitary Government agencies were (1) the Bureau of Entomology and Plant Quar-

<sup>16</sup> Craigie, James: Application and Control of Ethyl-Ether-Water Interface Effects to the Separation of Rickettsiae From Yolk Sac Suspensions. Canadian J. Research 23, Section E: 104-114, June 1945. (Manuscript was submitted on 9 Feb. 1942, but was withheld from publication for security reasons.)

<sup>17</sup> Report, Col. Harry Plotz, MC, for the Director, United States of America Typhus Commission, 18 Jan. 1946, subject: Report on Contributions From the Division of Virus and Rickettsial Diseases, Army Medical School, on the Development of the Typhus Vaccine.

<sup>18</sup> Topping, N. H., and Shear, M. J.: Studies of Typhus Fever Vaccines. Section III. Studies of Antigens of Infected Yolk Sacs. Nat. Inst. Health Bull. No. 183: 13-17, 1945. (This Bulletin contains reports that had been withheld from publication for security reasons.)

antine, U.S. Department of Agriculture; (2) the Division of Pharmacology of the Food and Drug Administration, Federal Security Administration; (3) the International Health Division, Rockefeller Foundation; and (4) the National Institute of Health, U.S. Public Health Service. The studies were coordinated by the National Research Council and the Committee on Medical Research, Office of Scientific Research and Development. In April 1942, the facilities at the Orlando, Fla., Laboratory of the Division of Insects Affecting Man were expanded for this work.<sup>19</sup> In the laboratories of the Divisions of Insecticide Investigations and Control Investigations of the U.S. Department of Agriculture at Beltsville, Md., increased attention was given to problems of military importance.

The subjects of insecticide (lousicide) research, development, and application are treated in portions of other volumes of this series by Colonels Hardenbergh,<sup>20</sup> Callison,<sup>21</sup> and Whayne.<sup>22</sup> Only a short account and commentary will be presented here.

**Insecticide (lousicide) powders.**—At the beginning of 1942, the Army had available for the control of body lice an insecticidal powder containing rotenone and pyrethrins. It was only moderately effective. In the search for new compounds and new combinations of ingredients, an extensive screening process was put into operation. Most of the work was done at the Orlando Laboratory where a large colony of lice (25,000 to 75,000) was maintained and many human beings were employed as subjects for the feeding of the lice and for tests. The objective was to find a substance or combination of substances which when applied to the skin or clothing would kill lice and their eggs rapidly and would persist for some days at the site of application exerting a residual effect. Before the advent of DDT, the objective was partly attained through the finding that purified nonirritating pyrethrins could be given greater activity as the toxicant by using *n*-isobutylundecylenamide as a synergist, and the finding that 2,4-dinitroanisole was a good ovicide for killing louse eggs. The stability of the pyrethrins was improved by the addition of an antioxidant, phenol S. The diluent, or carrier powder, was micronized pyrophyllite. The preparation composed of these substances finally recommended by the Bureau of Entomology and Plant Quarantine through the Orlando Laboratory and through the National Research Council on 18 August 1942 was known as MYL.

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<sup>19</sup> Haller, H. L., and Cristol, S. J.: The Development of New Insecticides. *In* *Advances in Military Medicine*. Boston: Little, Brown, and Co., 1948. vol. II, ch. XL, pp. 621-626.

<sup>20</sup> (1) Hardenbergh, William A.: Control of Insects. *In* Medical Department, United States Army. *Preventive Medicine in World War II. Volume II. Environmental Hygiene*. Washington: U.S. Government Printing Office, 1955, pp. 231-232. (2) Hardenbergh, William A.: The Research Background of Insect and Rodent Control. *In* Medical Department, United States Army. *Preventive Medicine in World War II. Volume II. Environmental Hygiene*. Washington: U.S. Government Printing Office, 1955, pp. 251-269.

<sup>21</sup> Callison, Robert L.: Personal Hygiene. *In* Medical Department, United States Army. *Preventive Medicine in World War II. Volume III. Personal Health Measures and Immunization*. Washington: U.S. Government Printing Office, 1955, pp. 24 and 26.

<sup>22</sup> Whayne, Tom F.: Clothing. *In* Medical Department, United States Army. *Preventive Medicine in World War II. Volume III. Personal Health Measures and Immunization*. Washington: U.S. Government Printing Office, 1955, pp. 57-58.



On 19 August 1942, Colonel Stone, writing for The Surgeon General, recommended to the Chief of Engineers that MYL be adopted, procured, and issued in place of the powder then in use.

At this time, the Chief of Engineers was charged with the responsibility for procurement and issue of insecticidal powders against body lice under his project for repellents against flying insects, which was a portion of his responsibility for the "execution of insect control programs including ditching and drainage." Fortunately, these incongruous arrangements were changed gradually during the year and finally in August 1943,<sup>23</sup> when The Surgeon General was made responsible for specifications, and the Quartermaster Corps was made responsible for requirements, funds, purchase, inspection, storage, and issue. AR (Army Regulations) 40-205, 31 December 1942, placed new emphasis upon the use of insecticidal powder for the control of body lice. It advised that the approved Quartermaster Corps issue be dusted into the seams of clothing every 7 to 10 days, not only as a delousing measure but as a prophylactic against infestation.

As a rule, louse powder was issued in 2-ounce shaker cans labeled "Insecticide Powder for Body Crawling Insects." As the labels never carried a statement of the composition of the powder, the user in the field did not always know what any particular can contained. MYL (pyrethrins) came into increasing use toward the end of 1942 and until the fall of 1943 when it was replaced gradually by DDT.

The work that led to the adoption of DDT began in 1942. The initials DDT stood for the relatively simple compound, dichlorodiphenyltrichloroethane. It was synthesized in 1874 by Othmar Zeidler, a young German student of chemistry at Strasbourg, in connection with his thesis on chlorinated phenyl compounds. The formula remained in obscurity in a chemical journal for nearly 70 years before its biological properties were tested. For some 10 years before 1939, the J. R. Geigy Company of Basel, Switzerland, had been working on insecticides. Their chemists, especially Drs. P. Lauger and P. Müller, found that the water-insoluble, fat-soluble compound, DDT, had extraordinary activity against insect pests and parasites of man and animals. It was recognized as a contact poison, lethal in minute amounts to a great variety of insects, and possessing a prolonged residual effect—up to 6 weeks—when applied to walls, screens, clothing, and skin. It was not an ovicide, but this did not matter because the residual effect killed off successive crops of nymphs as they emerged from eggs. The Geigy Company patented the material and made it the active ingredient of Neocid (or Gesarol), the lousicidal effect of which was known to members of the company's staff and Dr. H. Mooser,<sup>24</sup> typhus expert. Dr. Mooser's tests of Neocid as a lousicide were made at his Institute of Hygiene at the University of Zurich early in 1942, and in a speech

<sup>23</sup> (1) War Department Circular No. 69, 7 Mar. 1942. (2) War Department Circular No. 178, 7 Aug. 1943.

<sup>24</sup> Mooser, H.: Die Bedeutung des Neocid Geigy für die Verhütung und Bekämpfung der durch Insekten übertragenen Krankheiten. Schweiz. med. Wchnschr. 74: 947, 1944.



in Geneva, on 18 September 1942, on typhus fever, Dr. Mooser reported on his laboratory experiments with Neocid on body lice and spoke of the possibilities apparently offered by the preparation for the control of typhus epidemics. The Geigy Company, in August 1942, informed the American and British attachés in Switzerland about the remarkable insecticidal properties of DDT. In October or November 1942, the Geigy Company's New York branch gave the Orlando Laboratory of the Bureau of Entomology and Plant Quarantine, U.S. Department of Agriculture, a small sample of Neocid. At Orlando, the active ingredient, DDT, was isolated and synthesized,<sup>25</sup> and by the end of 1942, the extraordinary potency of DDT as an insecticide was confirmed. Steps were taken immediately to develop a louse powder containing DDT for use in the Army.

Following these laboratory discoveries and forecasts of the usefulness of DDT for malaria control, typhus control, fly control, and control of bedbugs, roaches, and fleas, enormous activities of military, political, and economic significance developed. DDT, in short supply, was in great demand both locally and internationally. For the next 3 years the Preventive Medicine Service and the U.S.A. Typhus Commission were at the center of these affairs.

**Delousing by fumigation.**—Anyone who has had any experience with steam disinfestors recalls the clumsiness of the heavy apparatus, the difficulty or impossibility of handling it in the field with troops in movement, and its shriveling effect upon clothes, shoes, and any shrinkable equipment. Realizing that something better was needed, Major Stone, soon after his arrival in the Preventive Medicine Service in 1941, initiated work on the replacement of steam by a fumigant to kill lice and their eggs without damaging clothing and equipment, and which could be applied by light apparatus. Methyl bromide<sup>26</sup> was selected. Under the direction of Major Stone, research and developmental work was done at the Agricultural Research Center at Beltsville, Md.

Three methods of application were developed: (1) Vault fumigation, in which quantities of bagged clothing were exposed to methyl bromide vapor in a gastight vault or plywood chamber; (2) individual bag fumigation, in which one soldier's outfit was exposed in a gastight fumigation bag; and (3) pit fumigation, in which from one to many bags were fumigated in a pit dug in the ground.

During 1942, this fumigation method came into limited use in the Army. In the field, where lousiness was readily controlled by louse powder, fumigation was little used. It was used chiefly in the North African-Mediterranean Theater of Operations in 1943 and 1944 when Colonel Stone was the preventive medicine officer of that theater.<sup>27</sup> In the continental United States, the chief use of the method was at ports of embarkation and debarkation.

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<sup>25</sup> Bushland, R. C., McAlister, L. C. Jr., Eddy, G. W., and Jones, H. A.: DDT for the control of Human Lice. *J. Econom. Entomol.* 37: 126-127, February 1944.

<sup>26</sup> Circular No. 745, U.S. Department of Agriculture, Washington, D.C., April 1946, subject: Methyl Bromide as a Delousing Agent.

<sup>27</sup> Circular Letter No. 43, Office of the Surgeon, Headquarters, North African Theater of Operations, U.S. Army, 11 Nov. 1943, subject: Typhus Fever Control.

## REORGANIZATION OF THE ARMY—RELATIONS WITH ARMY SERVICE FORCES

During 1942, the Army was reorganized in accordance with War Department Circular No. 59, 2 March 1942. This created SOS (Services of Supply), later named ASF (Army Service Forces), and placed The Surgeon General under the jurisdiction of the Commanding General, ASF, although direct access to the Secretary of War by The Surgeon General was still a possibility in certain circumstances. The Preventive Medicine Service was thereby brought into close connection with a medical section of ASF, the Hospitalization and Evacuation Branch, and also with its International Division. This connection with ASF became particularly important during the staff work on the establishment of the U.S.A. Typhus Commission and throughout its existence. While many disadvantages resulted from the subordination of The Surgeon General and the Medical Department to ASF, the arrangements were not too disturbing to the disease-control programs of the Preventive Medicine Service. Indeed, in many situations, it was advantageous for those activities of prevention and control that involved the administration of the Army as a whole. Furthermore, through this relationship, many international transactions essential for worldwide typhus control were greatly facilitated.

**Investigation of the Medical Department.**—The Committee to investigate the Medical Department, particularly the Office of The Surgeon General, was appointed by the Secretary of War late in August 1942, at the instigation of the Commanding General, ASF. It rendered its final report and recommendations on 24 November 1942. Discussion of the report of this Committee appears in a volume <sup>28</sup> by Blanche Britt Armfield in the series for administrative history. Brief mention is made here of the consequences for military preventive medicine, including typhus control. In general, the Preventive Medicine Service was commended, but the Committee pointed out the need for more knowledge about the occurrence of disease in foreign countries in which U.S. Army troops might be deployed. As a result, the Preventive Medicine Service was able to strengthen its Medical Intelligence Division, and this became increasingly serviceable for typhus control.

## PRODUCTION OF TEXTS

A large part of the time of the staff of the Preventive Medicine Service was occupied by the preparation of texts of military publications, a number of which were concerned with typhus. The Medical Intelligence Division collected and disseminated information about communicable diseases and economic and social conditions in foreign countries. Army Regulations, including requirements and information for typhus control, were revised. AR 40-210,

<sup>28</sup> Medical Department, United States Army. *Organization and Administration in World War II.* Washington : U.S. Government Printing Office, 1963.

"Prevention and Control of Communicable Diseases of Man," and AR 40-205, "Military Hygiene and Sanitation," were issued on 15 September 1942 and 31 December 1942, respectively. The text of Circular Letter No. 33, Office of The Surgeon General, "Treatment and Control of Certain Tropical Diseases," was prepared, but it was not issued until 2 February 1943. A considerable amount of the latest information about typhus control was included in these publications.

## BEGINNINGS OF CONTACT WITH TYPHUS OVERSEAS, 1941-42

The first contacts between the Preventive Medicine Service and epidemic typhus in the field began in 1941 when U.S. Army military missions and some theaters of operations overseas were established. Activities along these lines increased greatly in 1942.

**Atlantic bases.**—The rumor that epidemic typhus had been introduced into Jamaica, B.W.I., in 1941 by U.S. Army troops was quashed by the work of Plotz<sup>29</sup> and his coworkers who proved that the disease was murine typhus, endemic on the island.

**Air transport route across Africa and U.S. Army Forces in Central Africa.**—In 1941, the Preventive Medicine Service became concerned with problems of typhus in Africa through informal association with medical representatives of Pan American Airways, which, at the request of the U.S. Government, was engaged in setting up an air transport route across central Africa. The Army began to take over this route in January 1942, and the transfer was completed in December. During the year, a theater force known as the USAFICA (U.S. Army Forces in Central Africa) was established.<sup>30</sup> At first, the main places on the route were Accra, Khartoum, and Cairo. Later, the route was extended from Cairo to Karāchi, India, via Aden. The mere mention of these places indicates a route spotted with typhus.

**U.S. Military North African Mission and Middle East theater.**<sup>31</sup>—To aid the British in the management of the lend-lease program, the U.S. Military North African Mission was maintained from 22 November 1941 until 19 June 1942. On the latter date, it was abolished, and in its stead, USAFIME (U.S. Army Forces in the Middle East), with Headquarters at Cairo, Egypt, was established. A large part of the vast territory which the Middle East theater encompassed (p. 205) was the homeland of typhus. Fortunately, the chief medical officer of the original Mission who became Chief Surgeon of the Middle East theater was Maj. (later Brig. Gen.) Crawford F. Sams, MC, whose support and enforcement of measures for typhus control during World War II were notable.

Epidemic typhus was prevalent throughout the Middle East, and many thousands of native laborers who were louse infested were employed in the

<sup>29</sup> See footnote 14, p. 188.

<sup>30</sup> Annual Report, Surgeon, Headquarters, U.S. Army Forces in Central Africa, 1942.

<sup>31</sup> Annual Report, Surgeon, Headquarters, U.S. Army Forces in the Middle East, 1942.



midst of American troops on numerous types of projects. During 1942, among the Egyptians, about 24,000 cases of epidemic typhus with some 3,000 deaths were reported—the largest epidemic of typhus that had occurred in Egypt in more than 10 years (table 34). During this time, only one mild case of typhus fever occurred among U.S. Army troops in the theater. These troops had been vaccinated against typhus, were supplied with louse powder (pyrethrum and rotenone), and were provided with facilities for bathing and steam disinfection.

In Iran, epidemic typhus smoldered throughout the land and occasionally flared up from December through April. U.S. Army troops were exposed to infection chiefly at Abadan and at Teheran. Table 34 reveals that 1,102 cases were reported among the Iranians in 1942, and more than 12,000 in 1943. There were fewer than eight mild cases among American units in Iran.

TABLE 34.—*Epidemic typhus in French North Africa, Egypt, and Iran, 1930–44*

Year	Number of reported cases		
	French North Africa	Egypt	Iran
1930.....	529	288	-----
1931.....	930	265	1, 167
1932.....	965	2, 298	1, 544
1933.....	1, 671	7, 865	327
1934.....	1, 456	7, 536	1, 212
1935.....	1, 977	3, 151	619
1936.....	2, 182	2, 757	202
1937.....	8, 921	2, 083	116
1938.....	11, 377	2, 867	16
1939.....	9, 353	4, 239	89
1940.....	3, 547	4, 135	256
1941.....	21, 726	9, 324	115
1942.....	77, 335	23, 941	1, 102
1943.....	27, 340	40, 084	12, 885
1944.....	6, 226	18, 533	6, 436

Source: (1) Grenouilleau, G.: L'Epidémie de typhus en Algérie (1941–1942–1943). Arch. Inst. Pasteur d'Algérie 22 353–379, December 1944. (2) Stowman, K.: Typhus During the War. Epidemiol. Inform. Bull. 1 (7): 321, 30 April 1945 (3) See footnote 32.

A special feature of the situation in Iran in 1942 was the outbreak of epidemic typhus among Polish refugees. According to Brigadier A. Sachs,<sup>32</sup> R.A.M.C., who was Assistant Director of Pathology, British Persia-Iraq Force:

In the spring of 1942, some 28,000 Polish refugees and soldiers evacuated from Russia arrived in Iran via Pahlevi, a port on the Caspian coast. Typhus was stated to have been

<sup>32</sup> Sachs, A.: Typhus Fever in Iran and Iraq, 1942–43. A Report on 2,859 Cases. J. Roy. Army M. Corps 86: 1–11, 87–108, 1946.

rife in the concentration camp from which they came. Malnutrition was marked. The strictest measures were taken to prevent the spread of the disease. All refugees were disinfested on arrival at the port and again at Teheran where they were segregated from the local populace. Cases of typhus occurred shortly after disembarkation. It is improbable that any cases contracted the disease after leaving the port of arrival. In view of the strict measures adopted, and the early cessation of new cases, it is unlikely that this imported typhus had any bearing on the outbreak that occurred among the civil population of Iran during the ensuing winter.

**China-Burma-India theater, 1942-45.**—As operations for the control of epidemic typhus in this theater did not become extensive, the whole experience from 1942 to 1945 will be summarized here, although this will put the account ahead of its plan.

With the inception of the China-Burma-India theater in February-March 1942, U.S. Army troops became exposed to epidemic typhus in China. The consolidated theater existed from 4 March 1942 to 24 October 1944. On 24 October 1944, it was divided into the China theater, with headquarters at Chungking, and the India-Burma theater with headquarters at New Delhi. The 63 cases of epidemic typhus shown in table 33 to have occurred in "China-Burma-India" were cases among U.S. Army troops in China. There were no cases of epidemic typhus among such troops in the India-Burma theater, nor were there any reports of lousiness among these troops.<sup>33</sup>

**The China theater.**—In addition to the statistics just presented, there were several aspects of typhus in China which were of special interest.

As epidemic typhus was an ancient perennial among the recurrent diseases of China, it presented some relatively urgent problems to the civilian and military authorities of the Chinese Nationalist Government, to Lt. Gen. (later Gen.) Joseph W. Stilwell, commanding combined Chinese and American Forces, and to Col. Robert P. Williams, MC, surgeon of the China-Burma-India theater. Seeking assistance, the Chinese Government, on 23 April 1943, invited members of the U.S.A. Typhus Commission to visit China. This invitation was duly accepted and the visit was approved by the War Department and the State Department. General Fox, Field Director of the U.S.A. Typhus Commission, and Lt. Col. A. G. Gilliam, MC, Senior Surgeon, U.S. Public Health Service, attached to the Commission, visited Chungking and other places in China between 5 September and 21 October 1943. As a result of this visit, about 1,400,000 doses of typhus vaccine were sent to China through a lend-lease transfer. Of this amount, 900,000 ml. were to be made available to the Chinese Army Surgeon General and 500,000 ml. for the use of Chinese civil agencies for immunization of medical and essential personnel. Arrangements of this type were renewed from time to time during the war.

Colonel Gilliam, who remained in China until early 1944 (when he contracted scrub typhus in Burma), made surveys of the typhus situation in Chungking and in the cities of Kweiyang, Ch'eng-tu, Sian, and Lanchow. Chinese investigators furnished a great deal of information about typhus in

<sup>33</sup> Van Auken, Howard A.: *A History of Preventive Medicine in the U.S. Army Forces of the India-Burma Theater, 1942-45*, 8 Dec. 1945. [Official record.]

the country. Dr. Liu Wei-Tung was brought to the United States via the U.S.A. Typhus Commission laboratory at Cairo, Egypt, for training in typhus research at the laboratories of the International Health Division of the Rockefeller Foundation, at the Rockefeller Institute, and at the National Institute of Health. Laboratory equipment and supplies were sent to China.

The area was not a sufficiently active theater of operations to warrant setting up a Field Headquarters of the U.S.A. Typhus Commission at Chungking, or elsewhere in China. In September 1945, Col. Thomas T. Mackie, MC, who was then Executive Officer of the U.S.A. Typhus Commission Field Headquarters at Myitkyina, Burma (a station engaged primarily in the study of scrub typhus), explored with Dr. P. Z. King, Director General, National Health Administration, China, the possibility of making a cooperative arrangement between the Commission, the Administration, and the United Nations Relief and Rehabilitation Administration for a program of typhus control in China. As the problems were essentially civilian, and as the war had ended, this proposal was not adopted, and contact ended at about this time.

**India-Burma theater.**—During the period 1942–45, there were several outbreaks of epidemic typhus among the civil population in India and some among Chinese troops who had entered the theater in the summer of 1944 or who had been flown “over the hump” into Assam. The chief outbreaks among civilians were at Srinagar in Kashmir in October 1943 and at Darjeeling in October 1944. Through the U.S.A. Typhus Commission and the Commanding General of the India-Burma theater, supplies of typhus vaccine and MYL louse powder were made available to civilian groups and British troops in the infected areas.

**South Pacific Area, 1942–45.**—Between March and December 1942, task forces were landed and stationed upon many Pacific islands east of the perimeter of Japanese occupations. Chief among these were the Fiji Islands, New Caledonia, and New Zealand. The task forces, reinforced, became USAFISPA (U.S. Army Forces in the South Pacific Area). No epidemic typhus was reported from any of these islands during the war.<sup>34</sup> The occurrence of murine typhus on some of them is discussed in part II.

**Southwest Pacific Area.**—U.S. Army Forces in Australia were constituted by 21 December 1941, and from this organization developed SWPA (Southwest Pacific Area) under Gen. Douglas MacArthur. SWPA included a vast region of ocean and islands from Australia and New Guinea to the Philippines. In this area, miteborne scrub typhus became second only to malaria as a severe affliction of troops, as described by Philip (ch. XI). There were a few cases of murine typhus. No case of epidemic typhus among U.S. Army personnel was reported from SWPA during the war.

Encounters with epidemic typhus in the Pacific area were entirely different when U.S. Army Forces entered Japan in August 1945. An account of the large epidemic that occurred in the first year of the occupation, 1945–46, will be presented later.

<sup>34</sup> Annual Report, Surgeon, South Pacific Area, 1942.



**European Theater of Operations, U.S. Army, 1942.**—From the vast records of ETOUSA (European Theater of Operations, U.S. Army), a few will be utilized here to present some events of 1942 which were particularly important for future programs of typhus control in North Africa and on the Continent.

The American Red Cross-Harvard Hospital Unit had come to England in July 1940, at the invitation of the British Ministry of Health, to work throughout the British Isles in preventive medicine and epidemiology. The director of the unit was Dr. John E. Gordon, Professor of Preventive Medicine and Epidemiology, Harvard University. In May 1942, this unit was activated by Col. (later Maj. Gen.) Paul R. Hawley, MC, Chief Surgeon, ETOUSA, as a medical general laboratory. Lt. Col. (later Col.) John E. Gordon, MC,<sup>35</sup> became Chief of the newly established Preventive Medicine Division, Office of the Chief Surgeon, ETOUSA, on 7 July 1942. Much is owed to Colonel Gordon's foresight and to his wise and vigorous direction of a large portion of the typhus control program in the European theater.

In July 1942, the Epidemiology Branch of this Division of Preventive Medicine became directly concerned with the planning for the invasion of North Africa, Operation TORCH. On 15 September 1942, its Chief, Maj. (later Col.) J. W. R. Norton, MC, was transferred to the staff of AFHQ (Allied Force Headquarters) for duty in preventive medicine in the coming North African campaign. This work occupied a great deal of the time of the staff of the Preventive Medicine Division, ETOUSA. However, as AFHQ took over all planning and much medical authority, official contact was interrupted between the two main expeditionary medical headquarters in London. Colonel Gordon practically ends his account of these matters with the September entry, as they had passed out of the ken of the European theater.

During the late summer and early fall of 1942 while Anglo-American planning for Operation TORCH was going on at AFHQ in London, Col. (later Maj. Gen.) Albert W. Kenner, MC, who had been selected by Gen. George S. Patton, Jr., to be Chief Surgeon of the Western Task Force destined to land on the Atlantic coast of French Morocco, was at work in Washington on medical planning and its correlation with the planning of the General Staff and Special Staff.<sup>36</sup> Colonel Kenner worked in close association with Col. William L. Wilson, MC, Chief, Hospitalization and Evacuation Branch, Plans Division, Services of Supply. He had relatively little connection with the Office of The Surgeon General. The writer recalls one or two secret planning meetings held in the Preventive Medicine Service, but believes that the exchanges of information were few and inadequate.

Uncertainties and lack of medical intelligence regarding typhus fever in North Africa and the Middle East influenced Colonel Simmons to take actions

<sup>35</sup> Gordon, John E.: *A History of Preventive Medicine in the European Theater of Operations*, U.S. Army, 1941-45, vol. I, pt. I, pp. 1-11. [Official record.]

<sup>36</sup>(1) Kenner, A. W.: *Medical Service in the North African Campaign*. Bull. U.S. Army M. Dept. No. 76, May 1944; and No. 77, June 1944. (2) Interviews, G. H. Wilson, and W. K. Daum, with Maj. Gen. Albert W. Kenner, 10 and 11 Jan. 1952, respectively.

in July and August 1942 that resulted in the establishment of the U.S.A. Typhus Commission (p. 200).

Judging by later disclosures, the information about typhus in North Africa available to the planners at AFHQ was inaccurate and incomplete. It led to the thought that there was not much typhus in Morocco and Algeria, while in fact one of the largest epidemics in recent times was in progress. More than 60,000 cases had been reported for the first 10 months of 1942, and probably five times as many more were unreported. Commenting on this, Long<sup>37</sup> wrote later:

In historical retrospect, the introduction in 1942-43 into North Africa of an American Force which soon numbered hundreds of thousands of men, at a time when the most severe epidemic of typhus fever the world had known in the last 25 years was raging, offers food for thought, because the spectacular use of DDT as a dusting powder has overshadowed the importance of the use of typhus vaccine in the prevention of typhus fever. A review of the facts shows that in a force of several hundred thousand American troops, which was introduced into North Africa and protected against typhus by vaccination, only nine cases of typhus were reported in 1943, and of these nine (all of which were mild) the diagnosis in at least five instances was in doubt. This is to be compared with the experience of the smaller British North African Force which was unprotected and in which more than 29 cases of typhus, with at least 12 deaths, occurred during the same period of time.

The details of this outbreak were published later by Chalke.<sup>38</sup>

This author would add the further statement that these U.S. Army troops were free from infestation with lice and were kept deloused by applications of lousicidal powders, by bathing, and by occasional steam disinfestation of clothing and equipment.

To emphasize the extent of the risk from typhus which surrounded the invading forces in the North African campaign from the landings on 8 November 1942 to the end of the fighting in Tunisia on 9 May 1943, the statistics of reported cases in natives and Europeans in French North Africa are presented in table 34. For convenience, similar figures for Egypt and Iran are included in this table.

Looking at the situation as a whole, one sees that in the year of the North African invasion the Allied Forces were in the midst of about 78,000 reported cases of epidemic typhus, and perhaps 500,000 additional unreported cases. Yet there were few infections among U.S. Army troops. There was no panic over the exposure and risks. Instead, there was confidence in the prescribed protective measures, and these were calmly applied. Later in 1943, after NATOUSA (North African Theater of Operations, U.S. Army) had been established, Colonel Stone, Chief Preventive Medicine Officer of the theater,

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<sup>37</sup> Report, Col. Perrin H. Long, MC, to Chief, Preventive Medicine Division, Office of The Surgeon General, subject: A Historical Survey of the Activities of the Section of Preventive Medicine, Office of the Surgeon, Mediterranean Theater of Operations, U.S. Army, 3 Jan. 1943 to 15 Aug. 1943, 10 Oct. 1945.

<sup>38</sup> Chalke, H. D.: Typhus: Experiences in the Central Mediterranean Force. Part I. *Brit. Med. J.* 1: 977-980, 29 June 1946. (Actually among these British troops there were 36 cases and 11 deaths from epidemic typhus—a case fatality ratio of 31 percent.)

and Dr. Fred L. Soper of the Rockefeller Foundation Health Commission used the prevalence of typhus fever as an opportunity for researches that resulted in a revolutionary improvement of typhus control—the mechanical dusting with DDT lousicidal powder of individuals fully clothed.

## THE UNITED STATES OF AMERICA TYPHUS COMMISSION

A separate book will be required to deal adequately with the voluminous records of the United States of America Typhus Commission. Fortunately, the papers reporting the scientific work of members of the Commission and of officers attached to it have been published in medical and scientific journals,<sup>39</sup> and a brief history of the start of the Commission was published in 1943.<sup>40</sup> At this point, a short account will be given of the establishment, powers, and certain activities of the Commission, without attempting to present a full and continuous history. In subsequent sections, its activities will be mentioned in connection with episodes of typhus in various areas and theaters to show its part in the general program of typhus control by the Army.

In July 1942, Col. (later Brig. Gen.) James S. Simmons, MC, Director, Preventive Medicine Service, realized that there was a disquieting insufficiency of information about the occurrence of epidemic typhus in North Africa, Egypt, the Middle East, and parts of Europe, including Germany, Poland, the Balkans, Rumania, and Soviet Russia. After a number of conferences with members of his staff and others, on 5 August 1942, Colonel Simmons submitted to The Surgeon General a proposed letter for transmission to the Chief of Staff through the Commanding General, Services of Supply, summarizing the state of affairs and recommending the formation of a group to be sent abroad to collect information on the basis of which an improved typhus control program could be built.

Although this was approved, much difficult staff work had to be done before final approval by the Secretary of War was obtained for the creation of a unit to be known as the United States of America Typhus Commission. Important in this achievement were Col. William L. Wilson, MC, Chief, Hospitalization and Evacuation Branch, Plans Division, Services of Supply; Col. (later Brig. Gen.) Robert C. McDonald, MC, of the same office; and Lt. Gen. LeRoy Lutes, GSC, Assistant Chief of Staff for Operations, Services of Supply. Later, General Lutes became a member of the Rear Echelon of the Commission and Chairman of the Commission's Executive Committee.

By 27 August 1942, a further statement by The Surgeon General expressed the enlarged conception that had been agreed upon at a conference in the Preventive Medicine Service on 22 August. Purposes, duties, powers, geographic areas of interest, and composition of the proposed unit were greatly enlarged.

<sup>39</sup>(1) United States of America Typhus Commission. Collected Reprints, Nos. 1-70, 1943-47. Washington: War Department. (2) A Symposium on the Rickettsial Diseases of Man. *In* Rickettsial Diseases of Man. Washington: American Association for the Advancement of Science, 1948.

<sup>40</sup>Bayne-Jones, S.: The United States of America Typhus Commission. *Army M. Bull.* 68: 4-15, July 1943.



As neither Colonel Simmons nor Dr. Dyer could be released to serve as Director of the proposed Commission, Capt. (later Rear Adm.) Charles S. Stephenson, MC, USN, was nominated for the post. He was appointed Director. Thereafter, he became the main spokesman and negotiator. Finally, after all approvals of the State Department and Federal Security Administration had been received, the Secretary of War approved the creation of the United States of America Typhus Commission. Captain Stephenson was appointed Director, and other members were appointed.

On 10 December 1942, the Secretary of War approved a Rear Echelon composed of the Assistant Chief of Staff for Operations, ASF, the Chiefs of the Preventive Medicine Services of the Army and Navy, and the Director of the National Institute of Health. Plans for future investigations by the Commission were discussed at a meeting of the Division of Medical Sciences of the National Research Council on 27 November 1942, and were recorded in the minutes of that meeting.

After prolonged discussions and consultations with governmental agencies concerned in this field, agreement was reached that the U.S.A. Typhus Commission should have high status, broad powers, and support by the War Department, Navy Department, State Department, U.S. Public Health Service, and all executive departments, independent establishments, and other Federal agencies. To effectuate this, President Roosevelt issued Executive Order No. 9285, on 24 December 1942, "Establishing the United States of America Typhus Commission." This order, which has been published in several places,<sup>41</sup> was as follows:

#### Executive Order No. 9285

##### Establishing the United States of America Typhus Commission

By virtue of the authority vested in me as President of the United States and as Commander in Chief of the Army and Navy of the United States, and for the purposes of protecting the members of the Armed Forces from typhus fever and preventing its introduction into the United States, it is hereby ordered as follows:

1. There is hereby established in the War Department, under the supervision and direction of the Secretary of War, a commission to be known as the United States of America Typhus Commission, hereinafter referred to as the Commission. The Commission shall serve with the Army of the United States, and shall consist of a Director, appointed by the Secretary of War, such officers of the Army Medical Corps as may be detailed as members thereof by the Secretary of War, such officers of the Navy Medical Corps and the Public Health Service as may be detailed as members thereof, upon request of the Secretary of War, by the Secretary of the Navy or the Federal Security Administrator, and such other persons as may be appointed as members thereof by the Secretary of War.

2. The Director of the Commission is authorized and directed to formulate and effectuate a program for the study of typhus fever and the control thereof, both within and without the United States, when it is, or may become, a threat to the military population. The operations of the Commission abroad shall be carried out in collaboration with the Department of State.

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<sup>41</sup>(1) Federal Register 7: 10899, 1942 (No. 253, December 1942), Executive Order No. 9285, "Establishing the United States of America Typhus Commission." (2) War Department Bulletin No. 3, Sec. II, 13 Feb. 1943. (3) Army M. Bull. 68: 4-5, July 1943.

3. The Director of the Commission is authorized to employ necessary technical and nonprofessional personnel, and to make such expenditures, within the limits of funds made available to the Commission by the War Department, Navy Department, United States Public Health Service, or other Governmental agencies, as may be deemed necessary by him to accomplish the purposes of this order. Members of the Armed Forces may be detailed for duty with the Commission.

4. The Director shall take steps to secure the cooperation, assistance, and services of other Governmental agencies; make arrangements for the visiting by members of the Commission of such areas of neutral or Allied Nations as may be necessary to further the study of typhus fever; arrange for the analysis, study, and publication of scientific data and material obtained in such field investigations; establish and maintain typhus fever study units at appropriate Governmental laboratories; and procure such laboratory space, clinical facilities, and equipment as may be necessary to accomplish the purpose of this order. He shall collaborate with the Secretary of War, the Secretary of the Navy, the Administrator of the Federal Security Agency, and appropriate civilian organizations, when necessary, regarding the procurement of personnel and equipment in connection with the activities of the Commission, keep the Secretary of War informed in regard to progress made in carrying out this order, and perform such other duties as from time to time the Secretary of War may assign to him.

5. All Executive departments, independent establishments, and other Federal agencies are hereby authorized and directed to assist the Secretary of War and the Director in carrying out this order, including the furnishing of equipment, transportation, and personnel facilities and assistance.

6. There is hereby established a United States of America Typhus Commission Medal, with suitable appurtenances, which shall be awarded by the President of the United States or at his direction, to any person who may render or contribute meritorious service in connection with the work of the Commission.

FRANKLIN D. ROOSEVELT.

THE WHITE HOUSE, *December 24, 1942.*

By this unusual Presidential order, the Commission was endowed with unprecedented authority to deal with the problems of a single group of diseases. It was one of the first composite military units. Some phases in its enabling order could be interpreted as directing it to intervene in situations over which another governmental agency (the U.S. Public Health Service) had statutory jurisdiction. Without funds of its own, the costs of operation of the Commission and the large expenditures for antityphus supplies which it recommended were paid by the various military organizations with which it was associated, and from lend-lease funds through OLLA (Office of Lend-Lease Administration) or FEA (Foreign Economic Administration), or UNRRA (United Nations Relief and Rehabilitation Administration). There was never any assembling of the figures for the costs of operation of the Commission or of expenditures made on the basis of its requests and recommendations. This author, former Director of the Commission, estimates that the direct costs of the Commission were nearly \$3 million and that the expenditures as a result of requests and recommendations amounted to at least \$10 million.

As a "miscellaneous activity" of the War Department,<sup>42</sup> having direct access to the highest governmental and military levels, the Commission was a

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<sup>42</sup> (1) War Department Circular No. 5, 4 Jan. 1944. (2) Army Regulations 345-5, 5 Aug. 1944. (3) War Department Circular No. 427, 2 Nov. 1944.

semiautonomous organization among the medical establishments of the Army. It was attached to, or accommodated in, various regular medical organizations, but it maintained its integrity as a War Department agency, established its own channels of communication, and handled its personnel through the Office of The Adjutant General or some echelon of the General Staff.

To facilitate the work of the Commission in theaters of operations overseas, letters were sent by order of the Secretary of War to commanding generals of such theaters, citing the Executive Order No. 9285, explaining the nature and purposes of the Commission, and requesting cooperation and assistance, particularly with respect to paragraph 5 of the Executive order. In a theater of operations, the members of the Commission and associated personnel were under the limited jurisdiction of the theater commander. Usually, the Field Headquarters of the Commission was attached to the Office of the Chief Surgeon, but in the European theater, it was attached to G-5 (civil affairs/military government), SHAEF (Supreme Headquarters, Allied Expeditionary Force). Although there were troubles from time to time, the necessary arrangements were worked out with sufficient harmony and effectiveness, on the whole. Naturally, the Commission took care to respect the regular medical and military authority and jurisdiction with which it was in contact. Indeed, it could not have functioned otherwise, presidential Executive order to the contrary notwithstanding.

### Personnel, Staffing, and Stations

During the period from 24 December 1942 to 30 June 1946, 75 commissioned officers, 6 civilian scientists and physicians, and about 200 enlisted men and women served with the U.S.A. Typhus Commission. The officers were drawn from the three services as follows:

1. From the U.S. Army: 49 (MC, 24; SnC, 14; MAC, 7; miscellaneous branches, 4).
2. From the U.S. Navy: 19 (all MC).
3. From the U.S. Public Health Service: 7.

The Headquarters, Field Headquarters, teams, and their staffs were as follows:

*Washington, D.C.*—Headquarters of the Commission, located in Preventive Medicine Service, Office of The Surgeon General, U.S. Army. Opened 24 December 1942, closed 30 June 1946. Total staff of 25 officers over the entire period, with usually 3 to 5 in the office. From late October to about the end of 1942, before the issuance of Executive Order No. 9285, Admiral Stephenson conducted the affairs of the Commission from an office in the Preventive Medicine Division of the Bureau of Medicine and Surgery of the U.S. Navy.

*Cairo, Egypt.*—Field Headquarters in USAFIME (U.S. Army Forces in the Middle East). Opened 7 January 1943 with attachment to the Office of the Chief Surgeon, USAFIME; closed 25 September 1945, but through a liaison officer, U.S.A. Typhus Commission activities at Cairo were continued



and were officially terminated on 21 February 1946. The staff varied: usually about 8 to 10 officers.

*Naples, Italy.*—U.S.A. Typhus Commission Typhus Control Team, based in Cario and associated in Italy with NATOUSA-MTOUSA, AFHQ, and Allied Control Commission. First contact with typhus in Naples about 7 December 1943; participation in epidemic control from 20 December 1943; officially responsible for control from 3 January to 9 February 1944. Staff of six officers.

*London, England.*—Field Headquarters in ETOUSA (European Theater of Operations, U.S. Army) had connections with the Office of the Chief Surgeon, ETOUSA, but was attached to Headquarters, SHAEF (G-5). Office opened 17 May 1944, closed 9 November 1944. Staff of seven officers.

*Paris, France.*—Field Headquarters in ETOUSA. Opened 9 November 1944, closed 27 August 1945. Staff of seven officers.

*Frankfurt, Germany.*—Field Headquarters in USFET (U.S. Forces, European Theater). Opened 27 November 1945, closed 22 April 1946. Staff of seven officers.

*New Guinea and the Philippines.*—Field Headquarters of mobile research and control teams concerned chiefly with scrub typhus:

1. Joint team with the Army Epidemiological Board, in Eastern New Guinea, SWPA, from 19 October 1943 to 12 December 1943. Staff of three officers.

2. Group with troops in New Guinea and the Philippines, SWPA, from 7 April 1944 to 19 March 1945. Staff of four officers.

*Manila, P.I.*—Field Headquarters in SWPA (Southwest Pacific Area), later USAFPAC (U.S. Army Forces, Pacific). Opened in attachment to the Office of the Chief Surgeon, 19 March 1945, closed about 23 October 1945, when USAFPAC-Rear moved to Tokyo, Japan. Staff of seven officers.

*Tokyo, Japan.*—Field Headquarters in USAFPAC-Advanced, with attachments to Office of the Chief Surgeon, General Headquarters, USAFPAC, and to Public Health and Welfare Division, SCAP (Supreme Commander for the Allied Powers). Opened 3 October 1945, closed 20 May 1946. Staff of nine officers.

*Myitkyina, Burma.*—Field Headquarters in CBI (China-Burma-India theater) was attached to the Office of the Chief Surgeon of the theater. Opened 9 November 1944, closed 10 November 1945, was concerned chiefly with problems of scrub typhus in the Ledo Road area. Staff of 18 officers.

In the staff enumerations just given, the total of officers assigned to stations and teams exceeds the total assigned to the Commission. The explanation is that a number of officers served at various times at more than one station, and they were counted for each assignment.

The Directors of the U.S.A. Typhus Commission were:

Rear Adm. Charles S. Stephenson, MC, USN, originally designated Director on 22 October 1942, formally appointed Director on 13 January 1943, and relieved as Director on 17 February 1943 on account of illness.

Brig. Gen. Leon A. Fox, MC, appointed Director on 17 February 1943 (while in grade of colonel), at his request relieved as Director on 21 August 1943 and appointed Field Director.

Brig. Gen. Stanhope Bayne-Jones, MC, appointed Director on 21 August 1943 (while in grade of colonel), relieved as Director, 30 June 1946, on termination of the Commission.

In all of these places and under all sorts of conditions, the relationships between the Commission and organizations, and between individuals, were intricate, often experimental, and sometimes difficult. While they were harmonious on the whole, controversies and conflicts occurred occasionally. The most serious of these were in the Field Headquarters of the Commission at Cairo in 1943, and between the Commission and the Preventive Medicine Division of the Office of the Surgeon of the North African-Mediterranean Theater of Operations. Conflicts and mutual recriminations, however, did not prevent great accomplishments. There was ample credit for all, although it was not always widely accorded at the time. Regretting that such troubles occurred at all, the author will limit the mention of them to a few that seem sufficiently important and will try to avoid recall of bitterness.

The U.S.A. Typhus Commission had an eventful existence of about 3½ years until, on its own motion, it was dissolved as of 30 June 1946 by President Truman's Executive Order No. 9685, dated 17 January 1946.

## EPIDEMIC TYPHUS IN THE MEDITERRANEAN REGION, 1943-45

In spite of the vastness of the area and its many different countries and peoples, and in spite of the differences between the missions and military situations of the American and British organizations in the area, it is possible to present a fairly unified account of activities for the control of epidemic typhus in the Mediterranean region and Middle East from 1 January 1943 to 31 December 1945.

The two major theaters were:

1. USAFIME (U.S. Army Forces in the Middle East), later, 1 March 1945, AMET (the Africa-Middle East theater), which included Egypt, Palestine, Trans-Jordan, Lebanon, Syria, Turkey, Iraq, Iran, Saudi Arabia, Greece, Yugoslavia, and Senegal (Dakar), with minor contacts with Libya, Anglo-Egyptian Sudan, Ethiopia, Eritrea, British Somaliland, Italian Somaliland, Yemen, Aden Protectorate, and Oman.

2. NATOUSA (North African Theater of Operations, U.S. Army), later, 1 November 1944, MTOUSA (Mediterranean Theater of Operations, U.S. Army), which included Morocco, Algeria, Tunisia, Libya, Sicily, Italy, Yugoslavia, Turkey, Greece, and Spain.

The boundaries of these two theaters were changed from time to time. Hence the names of several countries appear in both jurisdictional lists.

The Africa-Middle East theater was never a theater of military combat. From the start in 1942, the chief concern of USAFIME, with Headquarters at Cairo, Egypt, was to give aid to the British war effort in that region. In July 1943, the strength of the Middle East theater reached a peak of 66,500, of which number 27,300 were in the Persian Gulf Command. By January 1944, the strength had dropped to 46,000. The U.S. Ninth Air Force left the theater in September 1944. By September 1945, the strength was 21,000. In 1943, the main functions of this theater became those of supply and service. Extensive lend-lease transactions were conducted there through FEA and the Middle East Supply Center, at Cairo.

### Typhus Commission Activities in USAFIME

The Forward Echelon of the U.S.A. Typhus Commission arrived at Cairo, Egypt, on 7 and 20 January 1943. The first section under Admiral Stephenson, Director, included Colonel Plotz (p. 188); Lt. Comdr. W. B. McAllister, MC, USNR; and Dr. Fred L. Soper, staff member of the International Health Division of the Rockefeller Foundation. The second section under Capt. E. H. Cushing, MC, USNR, included Colonel Gilliam (p. 196); Maj. (later Lt. Col.) John C. Snyder, MC; Dr. Charles M. Wheeler, entomologist, later commissioned major, SnC; and Lt. Comdr. Andrew Yeomans, MC, USNR.

There were seeds of later troubles in the composition of the Forward Echelon of the Commission. Navy personnel predominated in a group designated to assist in handling ashore a predominantly Army problem. The large representation of the International Health Division and International Health Commission of the Rockefeller Foundation (Soper, Snyder, and Wheeler) tended to make a group within the group with special ties to the parent civilian organization. Arrangements for payments of salaries and for separations "at the earliest date compatible with the mission of the United States of America Typhus Commission" emphasized the divided allegiance.<sup>43</sup>

The Commission was well introduced by a letter, dated 27 December 1946, by order of the Secretary of War, to the Commanding General, USAFIME, and this letter secured all necessary support during the next 2 years. The main problem was how to integrate a presidential commission under the Secretary of War and a Director clothed with broad powers, reporting directly to the Secretary of War, into the military organization of a theater of operations under a commanding general whose powers were virtually absolute. As there were no precedents to be followed, arrangements had to be worked out through experience. In the Middle East theater in July 1944, a theater commander attempted to assign the local unit of the Commission to his headquarters "in a

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<sup>43</sup> Letter, Rear Admiral C. S. Stephenson, Director, United States of America Typhus Commission, to Dr. W. A. Sawyer, Director, International Health Division, Rockefeller Foundation, 9 Dec. 1942, with reply from Dr. Sawyer, 14 Dec. 1942, attached thereto.



command line."<sup>44</sup> This was resisted locally and was definitely prevented by staff action in Washington, by order of the Secretary of War.<sup>45</sup>

On 12 January 1943, an agreement was made between the Commission and the Ministry of Public Health of the Egyptian Government through which the Commission obtained the use and control of a ward for clinical studies of typhus at the Abassia Fever Hospital and laboratory space at the Government Serum Institute, and privileges for the study of the pathology of typhus. In addition, the agreement provided for a controlled study of the efficacy of typhus vaccine and for an investigation of louse powders at Esbe Rameses and Bidsah.

On 24 January 1943, Admiral Stephenson, who was on his way to Teheran to make a survey of the typhus situation in Iran, became ill in Damascus. Because of this illness, the Secretary of War regretfully relieved Admiral Stephenson of the Directorship of the Commission.

On 8 February 1943, the Secretary of War appointed Col. (later Brig. Gen.) Leon A. Fox, MC, Director of the Commission. General Fox arrived in Cairo on 28 March 1943 and took over and reorganized the Field Headquarters there. At about the same time, the Rear Echelon at the Washington office assumed authority which it should have been exercising from the beginning. At his request, General Fox was relieved as Director and appointed Field Director on 21 August 1943, and on the same date, Col. (later Brig. Gen.) Stanhope Bayne-Jones, MC, was appointed Director of the Commission to serve at the Headquarters in Washington, in addition to his other duties as Deputy Chief of Preventive Medicine Service and Administrator of the Army Epidemiological Board.

**Surveys.**—During the period from January 1943 to September 1945, the U.S.A. Typhus Commission made surveys of the typhus situation and related economic and medical conditions in most of the countries of North and East Africa and the Middle East. These surveys furnished a great deal of serviceable information which was used by both military and civilian authorities. Important scientific, military, and governmental contacts were made in all countries visited.

**Middle East Supply Center.**—Throughout this period, 1943–45, the Headquarters of MESC (Middle East Supply Center) was at Cairo. While the Center was predominantly a British organization, the chief civilian American representative on its board had the rank of Minister. The enormous lend-lease transactions handled by the Center were mostly for American agricultural products, food, and medical supplies. In 1943, the MESC area included 18 countries and about 80 million people. Late in 1944 and early in 1945, Yugo-

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<sup>44</sup> Staff Memorandum No. 12, Headquarters, U.S. Army Forces in the Middle East, Cairo, Egypt, 10 July 1944, subject: Organization and Operation of Headquarters, U.S. Army Forces in the Middle East.

<sup>45</sup> Radiogram Message No. WARX 81526 (TAM 260 from CCS cite OCAC), 14 Aug. 1944, subject: Special Attachment of the Cairo Group of the United States of America Typhus Commission to Headquarters, AML (Balkans). [Part 2 of this message clearly defines the status of the Commission as a "miscellaneous War Department activity under the supervision of the Secretary of War."]

slavia and Greece came into the MESC area through the operations of UNRRA and AML Balkans, bringing the countries up to 20 and the population up to about 100 million.

In all these countries, epidemic typhus was a problem, in varying degrees. In some, it was a threat or hindrance to the war effort, or an increased burden upon liberating and occupying military forces. Hence, MESC was constantly concerned with the procurement and distribution of supplies for the control of typhus, chiefly vaccine and louse powder.

The Chief Surgeon of the Middle East theater and the Field Director of the U.S.A. Typhus Commission were members of the Executive Committee of MEMAC (Middle East Medical Advisory Committee), the recommendations of which influenced policy, procurement, storage, and distribution of medical supplies. The U.S.A. Typhus Commission became a main adviser.<sup>46</sup> The final position of responsibility of the Commission is indicated in the following excerpt from a MEMAC memorandum, dated 26 January 1945:

The U.S.A. Typhus Commission will meet all legitimate requests for typhus vaccine placed by Middle East Governments through the Middle East Supply Center. Typhus vaccine issued to Middle East Governments is issued free of charge and remains the property of the U.S.A. Typhus Commission until finally administered to an individual. Agencies to which vaccine is issued serve as agents of the U.S.A. Typhus Commission, to which they are responsible for proper storage and administration of vaccine to them.

Regarding the free distribution of typhus vaccine, information is given in paragraphs to follow about the First Cairo Conference of 22-26 November 1943.

The U.S.A. Typhus Commission recommended that in developing typhus immunization programs and estimates of requirements for vaccine, particular attention should be given to—

1. The group at greatest risk—doctors, nurses, hospital staffs, public health and sanitary personnel, police, jailers, and prisoners.
2. Personnel who are at risk and the deprivation of whose services would interfere with the war effort or disrupt the normal life of the community, especially transportation employees and employees of communication services.
3. Whole communities which for one reason or another required protection might be considered for mass vaccination.
4. Military personnel of neutral countries. For example, on the advice of the U.S.A. Typhus Commission, typhus vaccine was supplied through MESC for the Egyptian Army, the Iranian Army, and the Turkish Army.

The requirements for typhus vaccine based upon these considerations became enormous. From 1943 through 1945, more than 50 million ml. of American-made typhus vaccine were provided for the Middle East countries and for Morocco and Algeria. During one critical period when there were no other "firm orders," the estimates of need, tantamount to requisition, placed by the

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<sup>46</sup>(1) Minutes, Middle East Medical Advisory Committee, 29 Apr. 1943. (2) Minutes, Middle East Medical Advisory Committee, 23 July 1943, attached copy of telegram from Middle East Supply Center to British Embassy, Ankara, Turkey, 16 July 1943.

U.S.A. Typhus Commission helped to keep the manufacture of the vaccine going in the United States, thus holding together the immunized staffs of workers at the specialized plants.

With respect to louse powders, particularly preparations of DDT, a similar story could be told about the beneficial collaboration between the Office of the Chief Surgeon, USAFIME, the U.S.A. Typhus Commission, and MESC. Starting from a dribble of samples for testing in 1943, the requirements, periodically determined, for the Middle East pool reached 30 tons of pure DDT by April 1944 and 60 tons in 1945. In this area, the U.S.A. Typhus Commission became a main adviser on production, procurement, supply, and allocation of DDT and dusters for use in the prevention and control of typhus.<sup>47</sup>

**Egypt.**—Surveys in Egypt, together with the reports of Van Rooyen,<sup>48</sup> showed that typhus among the Egyptians in areas around Cairo and Suez, and in the Nile Delta, was a major problem of civilian preventive medicine. The epidemic period was from December to June, with a peak usually in April. The case fatality rate was about 15 percent. As shown in table 34, the most severe epidemics of typhus fever in Egypt in 15 years occurred in the period of 1942–44. Military preventive medicine, however, had no difficulty in coping with the threat represented by these outbreaks of typhus in the civilian environment of troops.

To assist the Egyptian Government, typhus vaccine and louse powder were provided in large quantities through MESC. There was a high incidence of epidemic typhus in the Egyptian Army. For example, in a total strength of 62,500 in 1943, there were 239 cases and 40 deaths from epidemic typhus. Through an agreement between the Field Director of the U.S.A. Typhus Commission and the Egyptian Surgeon General, dated 8 January 1944, training in the newer methods of typhus control was provided and sufficient typhus vaccine to immunize the whole force was made available.

**Iran.**—To safeguard the supply of oil and gasoline from the wells and refineries in the region of the Persian Gulf and to make sure that Iran remained sympathetic to the Allies, it was necessary to support that country and to keep its customary diseases in check. Of these diseases, typhus was in the front rank. The accounts of actions taken to control typhus in Iran from 1943 to 1945 fill hundreds of pages. Many of them are so fantastic that they resemble the adventures of Hajji Baba of Ispahan.

Conditions similar to those in Egypt were found in Iran where outbreaks of typhus of unusual severity occurred during the period 1943–44, as shown in table 34. In the midst of this, the incidence of typhus in American troops was negligible.

<sup>47</sup>(1) Minutes, Middle East Medical Advisory Committee, 3 Apr. 1945. (2) Memorandum, Director, United States of America Typhus Commission, for Maj. Gen. LeRoy Lutes, Assistant Chief of Staff, Operations, Headquarters, Army Service Forces, 14 June 1944, subject: DDT Supply for the United States of America Typhus Commission and CAD.

<sup>48</sup>Van Rooyen, C. E., Bowle, J. H., and Krikorian, K. S.: Typhus Research in Egypt, Palestine, Iraq, and Iran. *Tr. Roy. Soc. Trop. Med. & Hyg.* 38: 133–149, November 1944.



Strenuous efforts were made by the U.S.A. Typhus Commission to organize a modern program of typhus control in Iran. It was difficult, however, to translate official agreements into actions, to apply principles and methods imparted in training, and to make sure that typhus vaccine and louse powders were administered as intended to essential personnel and to the louse-infested, typhus-bearing impoverished natives, and did not become sequestered by the politically prominent and wealthy, or peddled on the black market. By late 1944, vaccination against typhus and delousing with DDT had been carried out on a large scale. Vaccine and louse powder were supplied to the whole Iranian Army.

**Turkey.**—In 1943, Turkey was a source of anxiety because typhus increased to epidemic proportions and because there was the possibility that Turkey's "sympathetic neutrality" in relations with the Allies might be changed by German pressure to an attitude that would permit Axis counter-attacks through the Middle East to Suez at the time when the invasions of Sicily and Italy were getting underway. Ambassador Steinhardt appreciated the opportunity to bring American medical assistance to Turkey and thus strengthen the ties between the two countries.

According to Stowman,<sup>49</sup> in Turkey in 1940, 1941, and 1942, there were reported, respectively, 816, 950, and 878 cases of epidemic typhus fever. From the beginning of 1943, an increase became accelerated, and the epidemic reached a peak in April-June. Istanbul and the European territory of Turkey also were affected. In 1943, the total number of reported cases was 4,143; in 1944, the number was 3,261; and in 1945, it was approximately 3,000.

At the request of the Turkish Government, and with approval by the State Department and the War Department, Brig. Gen. Leon A. Fox, Director of the U.S.A. Typhus Commission, flew into Turkey (in civilian clothes), arriving at Ankara on 10 June 1943. He outlined a realistic typhus control program for Turkey and a special program for the Turkish Army, and gained an agreement for the conduct of two controlled field tests of typhus vaccine—one in the Army and one among the miners of the Zonguldak mines. Maj. (later Lt. Col.) Edward S. Murray, MC, was brought from the Commission's office at Cairo and put in charge of these activities. Typhus vaccine was supplied freely through MESC as a straight lend-lease transaction for use in immunizing civilians and the Army.

Unfortunately, for various reasons—some personal, some political, and some nationalistic—the efforts to carry out an orderly control program and scientific tests of the efficacy of the vaccine ended in disappointment. No conclusions could be drawn from figures collected during a year's work, although the Turkish authorities seemed to feel that the vaccine had prevented some occurrence of typhus. As conditions for scientific investigation remained unsatisfactory, the project was discontinued early in 1944. Although the scientific rapport lapsed, the political association had been strengthened.

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<sup>49</sup> Stowman, K.: Typhus During the War. *Epidemiol. Inform. Bull.* 1(7): 289-310, 30 April 1945.

**Field tests of MYL louse powder in Egypt in 1943.**—The U.S.A. Typhus Commission's work in Egypt on the study of MYL under conditions of natural louse infestation got underway in February 1943 at Esbe Rameses, a cluster of six homes lying just west of the Colossus of Rameses II on the site of ancient Memphis. This Esbe was administered by the nearby village of Mit Ruhaynah where the first field studies of the efficacy of typhus vaccine were made at a later date. On 4 March 1943, an outbreak of epidemic typhus at Bidsah, a village of some 2,000 people, 25 miles south of Cairo in the Province of Gizah, presented an opportunity to test the possibility of rapid control of typhus in an infected population.

By early March 1943, two rounds of application of MYL powder to clothing that had been removed from louse-infected persons and applications to the bodies of these persons were spectacularly effective. Dr. Soper<sup>50</sup> reported that the reduction of louse infestation in Rameses following the first two applications of MYL was most striking and suggested that complete cleaning of the population could be readily accomplished. As it turned out in the end, these were correct observations and valid conclusions. But a very troublesome period of acrimonious controversy, lasting nearly 6 months, had to be fought through before the argument was displaced by the greater interest in DDT.

To the dismay of the investigators, and many others, the third and fourth series of tests of MYL at Esbe Rameses in April and May 1943 gave irregular results and some failures. The investigators concluded that some batches or cans of MYL powder were defective or had deteriorated during storage.

Unfortunately, reports of these poor results and some indiscreet statements created the impression that the Army louse powder MYL was no good. Col. William S. Stone, MC, Chief, Sanitation Branch, Preventive Medicine Division, Office of The Surgeon General, a firm believer in MYL, severely criticized the design and conduct of the experiments of the Commission in Egypt. After much debate, retestings at Orlando, and review of records, the position maintained by Preventive Medicine Service was that the Commission's reports had aroused unwarranted criticism, that the Army's louse powder was effective, and that steps should be taken by General Fox to prevent or counteract unfavorable rumors based on incomplete information.

This controversy involved not only matters of morale but also policy as to whether reliance for delousing troops and civilians should be placed upon chemical insecticides in preference to disinfestation by heat. Passing over a great deal of searching debate and anticipating events, it may be said here that the decision made in Preventive Medicine Service early in 1944 was in favor of the use of chemical insecticides for delousing and for control of the louse factor in epidemics of typhus.

The outbreak of typhus at Bidsah, in March 1943, ended sooner than expected and with fewer than expected cases following applications of MYL

<sup>50</sup> Memorandum, Dr. Fred L. Soper, for Brig. Gen. Leon A. Fox, Director, United States of America Typhus Commission, 4 June 1943, subject: Appraisal of the Efficacy of Army Powder (MYL) and Methyl Bromide in the Control of Louse Infestation.

louse powder. This was regarded as a definite indication that an outbreak of typhus could be brought under control by application of a chemical insecticide.

**Mechanical dusters.**—The mechanical dusting of people fully clothed was highly important because of the saving of time and because of the impossibility, or great difficulty, of persuading Moslem women to disrobe. Unfortunately, there arose a dispute over priority of invention between the U.S.A. Typhus Commission and the Rockefeller team in North Africa, under the direction there of Dr. Soper who had been transferred to that assignment on 31 May 1943. The records show that as early as February and March 1943, Dr. Wheeler (p. 206), member of the U.S.A. Typhus Commission, was thinking about the use of agricultural hand dusters and power dusters for blowing louse powder up the sleeves, down the back, into the trousers or skirts, into the hair and hats, and into any clothing, bedding, equipment, floors, and furniture of persons infested with lice or suspected of being so infested. On 20 March 1943, in Cairo, he purchased a Signal Duster and a Corporal Duster for these purposes. Later in the year, he devised a motor-driven "power duster." In the North African theater, this method was perfected and priority claimed. This was another useless controversy. Others had had the same idea at least a year before. Notably Colonel Stone and Dr. John A. Farrell, Associate Director, International Health Division of the Rockefeller Foundation, had expressed the conception, in detailed terms, of delousing people fully clothed by puffing insecticide into their garments. In the opinion of this author, Dr. Wheeler was the first to apply MYL and later, in 1943, DDT louse powder mechanically by hand dusters and power dusters to louse-infested individuals fully clothed.

**Typhus vaccine tests.**—Tests of the efficacy of the Army's typhus vaccine were carried out by the U.S.A. Typhus Commission at the Abassia and Embaba Fever Hospitals in Cairo in 1943 and 1944. The published report on this work by Ecke<sup>51</sup> and his associates appeared in 1945, but the results were well known in the previous year.

In the first trial, conducted from January to July 1943, 743 individuals among Egyptian employees at the Abassia Fever Hospital were given one or more injections of the vaccine. In the second trial, from November 1943 to September 1944, 799 employees at Abassia and 460 at Embaba were given one or more doses of the vaccine. Among these 2,002 individuals who were exposed to typhus during two severe epidemics, 61 cases of typhus occurred. Most of the cases were mild. Only one death occurred, and that was of a person who had been vaccinated during the incubation period. The mortality in unvaccinated patients ranged from 8.7 to 47 percent, according to age. The results showed that, while vaccination did not always prevent infection, two or more doses of Cox-type vaccine given 3 weeks or more before the onset of typhus

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<sup>51</sup> Ecke, R. S., Gilliam, A. G., Snyder, J. C., Yeomans, A., Zarafonetis, C. J., and Murray, E. S.: *The Effect of Cox-Type Vaccine on Louse-Borne Typhus Fever. An Account of 61 Cases of Naturally Occurring Typhus Fever in Patients Who Had Previously Received One or More Injections of Cox-Type Vaccine.* *Am. J. Trop. Med.* 25: 447-462, November 1945.



reduced the severity of the illness and practically eliminated fatality. This experience strengthened the recommendation that vaccination against typhus be included in programs for the control of epidemics.

It was dreaded that individuals suffering from typhus subdued by vaccination would spread the disease among their louse-infested associates. Snyder<sup>52</sup> allayed these fears. He showed that "the lice which feed on patients who contract typhus after a course of typhus vaccine develop very few rickettsiae in comparison with lice from unvaccinated patients. Persons who have had booster doses infect their lice only rarely or not at all. Thus vaccination of a community undoubtedly will reduce the potentiality for spread of the disease by lice."

Several years later, after reviewing the evidence acquired from the experiences with typhus during World War II, Snyder summed up the opinion generally held as follows:

It seems safe to assert on the basis of the information now available that Cox-type vaccine when properly prepared and administered will reduce the mortality from typhus to a negligible point, will lessen the severity of the illness greatly, and should decrease enormously the possibility of typhus attaining epidemic proportions in a thoroughly vaccinated community.

**First notification of typhus in Naples.**—On 21 September 1943, BBC (British Broadcasting Company) announced that epidemic typhus fever was occurring in Naples, Italy. This was the first public flash from the gathering storm of typhus which became potentially dangerous to the Italian campaign of the Allied Forces from October 1943 to February 1944. On the date of the BBC broadcast, the Allied Forces were within 10 days of entering Naples. The account of actions preceding and following the uncovering of typhus in Naples will be given in the section dealing with the typhus control activities of the North African Theater of Operations.

**First Cairo Conference, 22–26 November 1943—free distribution of typhus vaccine.**—At the First Cairo Conference between President Roosevelt, Prime Minister Churchill, and Generalissimo Chiang Kai-shek, held from 22 to 26 November 1943, the President decided that the U.S. Government would distribute typhus vaccine without charge to Middle East countries. The President's decision, based upon a proposal submitted by General Fox, was stated as follows:

Typhus vaccine used for civil control of typhus fever in civil populations, as recommended and directed by the United States of America Typhus Commission, and under reasonable Typhus Commission control, to be made available from Typhus Commission stocks without reimbursement.<sup>53</sup>

The proposal for free distribution of typhus vaccine and measures to keep it out of the "black market" had been in the mind of General Fox for some

<sup>52</sup> Snyder, J. C.: Typhus Fever in the Second World War. California Med. 66: 1–10, January 1947.

<sup>53</sup>(1) Letter, Brig. Gen. Leon A. Fox, Field Director, United States of America Typhus Commission, courtesy of Admiral McIntire, for Col. S. Bayne-Jones, Director, United States of America Typhus Commission, 29 Nov. 1943. (2) Radiogram AMSME No. 9724, for Kirk inform Bayne-Jones from Fox signed Royce, 29 Nov. 1943.

time. He developed his ideas in conversations with Ambassador Steinhardt and Ambassador Winant, and General Lutes, in Cairo about 18–19 November, “as a program of typhus immunization for civil populations that would cost such a small percent of what we plan to spend for rehabilitation of civil populations in fought-over areas as to be relatively insignificant, and which would \* \* \* reflect credit on the American people.” Health agencies of foreign governments accepting the vaccine would, by agreement, act as official agents of the U.S.A. Typhus Commission and supervise the distribution locally. Ambassador Winant laid this plan before the President. It was discussed also with the Minister to Egypt, Mr. Kirk, and with the President’s physician, Admiral McIntire, who was *ex officio* a member of the U.S.A. Typhus Commission. The plan was approved by the President on 24–25 November 1943.

Shortly after the end of the Cairo Conference, arrangements were made by Headquarters of the Commission in Washington with OLLA and the Requirements and Supply Branch, Bureau of Supplies, FEA, to carry out this policy. The controlled free distribution of typhus vaccine to Middle East countries began early in December 1943, and after a final supply had been given to French Morocco and Algeria, it was terminated on 1 August 1945. It is estimated that approximately 20 million ml. of typhus vaccine was distributed under this system.

### North African-Mediterranean Theater of Operations

After the landings in French Morocco and Algeria on 7–8 November 1942, U.S. Army troops were engaged, with little respite, in major combat for the next 15 months, occasionally in the midst of the most severe epidemics of typhus that had beset the native populations in North Africa and Italy within the previous 10 to 20 years. Protected by vaccination and louse powder (at first MYL, later DDT), American troops fought through this environment of pestilence with little sickness and no deaths from typhus. As shown in table 33, during the period from 1942 to 1945, there were only 16 cases of typhus and no deaths from the disease among U.S. Army personnel in the North African-Mediterranean Theater of Operations. The troop strength was 260,000 in January 1943, 630,000 in October 1943, and was still about 500,000 in December 1944.

From the military point of view, the threat of typhus became alarming when the Fifth U.S. Army and other units of the Allied Forces entered devastated Naples, on 1 October 1943, without knowing that they were facing the beginning of an epidemic of typhus among the overcrowded, undernourished, louse-infested civilian population swelled by an influx of refugees. This hazard to the military campaign in southern Italy was overcome promptly by actions which are generally regarded as constituting one of the great triumphs of modern preventive medicine.

Before the history of the Naples epidemic is presented, it will be necessary to summarize important work done, and actions taken, in North Africa and else-



where from January to October 1943. This will be in addition to the preceding account of events that took place in USAFIME.

On 12 January 1943, contact was made by radiogram between the Field Headquarters of the U.S.A. Typhus Commission at Cairo and the Office of the Chief Surgeon of the U.S. Army Forces at Algiers. The Commission requested to be kept informed of the typhus situation in the North African theater. It is to be noted that no official notification concerning the Commission, such as had been sent to the Commanding Generals of ETOUSA and USAFIME, had been dispatched by the War Department to the Commanding General of the Allied Forces in North Africa. NATOUSA was not established until 3 February 1943. In the interim, command channels and communication between American and British jurisdictions were complicated and somewhat uncertain.

The Preventive Medicine Division, Office of the Chief Surgeon, North African theater, developed a strong typhus control program independently and chose the Rockefeller Foundation Health Commission Team, under the direction of Dr. Soper (p. 199), as its collaborating organization. The Commission was little, if at all, needed in NATOUSA in this period before Naples. Until the Naples epidemic appeared to be getting out of hand in December, the Commission was not called in officially.

On 6 February, the Office of the Chief Surgeon, NATOUSA, informed the Commission at Cairo that typhus was reaching epidemic proportions in Algeria. In response, members of the Commission made extensive surveys in French Morocco and Algeria and furnished useful information and advice. Unfortunately, in May, controversy arose over the use of chemical insecticides in place of steam disinfestation. In one of the survey reports, a lack of confidence in MYL had been expressed. This touched a sore spot and was an attack upon the preventive medicine policy then developing in favor of the use of insecticides for the control of body lice. Officers who had little or no faith in MYL, such as General Fox, Colonel Plotz, and Dr. Dyer, were not then convinced that it would be safe to discard the old methods and adopt the new insecticidal materials and procedures. On the other hand, Colonel Stone and others had increasing confidence in the use of insecticidal (lousicidal) powders. This difference of opinion was not settled until the clear-cut results obtained by Dr. Soper and his associates became known and until the experience at Naples had demonstrated that lice and an epidemic of typhus could be brought under control by dusting with insecticidal powders—MYL or DDT.

The opportunity for Dr. Soper's work in North Africa had been prepared in January 1943 by Dr. George K. Strode, Acting Director of the International Health Division of the Rockefeller Foundation. During his visit to Algeria in the company of Mr. Richard Allen of the American Red Cross, Dr. Strode made tentative arrangements through the American Minister, Mr. Robert D. Murphy, for the admission of a Rockefeller Foundation Health Commission Team to conduct studies on typhus among the native population. The objective was the study of the use of insecticidal powders for the control of body lice and typhus fever. The American Red Cross sponsored the studies which



had received the approval of the State Department. When Dr. Soper was detached from the U.S.A. Typhus Commission at Cairo on 31 May 1943, he moved to Algiers.

At Algiers, Dr. Soper established a relationship with the Office of the Surgeon, NATOUSA, where Colonel Stone was the Chief Preventive Medicine Officer. In June 1943, Dr. Soper was joined by three additional staff members of the Rockefeller Foundation Health Commission Team. The results of their work were reported currently, and in 1945, the whole was described in a comprehensive scientific publication.<sup>54</sup>

During the period from June to November 1943, the work of Dr. Soper and his associates included: "(1) Intensive studies carried out at the Maison-Carrée Prison near Algiers on the relative efficiency of factory-prepared MYL powder and powders containing DDT prepared with local excipients and applied by various methods; (2) the extensive field application of insecticide to the general population (male and female) of the town and commune of L'Arba in Algeria; and (3) a rapid field test in a prisoner-of-war camp of the new factory-prepared U.S. Army 10 percent DDT pyrophyllite powder."

Colonel Stone found that the results of this work were so promising by 28 August 1943 that he initiated a requisition for 10 tons of 10 percent DDT powder.

The powders and dusting implements used by Dr. Soper's group were: Louse Powders:

Army MYL Insecticidal Powder, QM Item No. 51-1-173.

DDT, mixed and ground with barytes (barium sulfate) or cement dust.

DDT Army Insecticidal Powder, 10 percent DDT in pyrophyllite.

QM Item No. 51-1-180: Insecticidal Powder Delousing.

Dusters:

Shaker tins.

Agricultural bellows dusters.

Hand dusters: Hudson Cadet-Major, plunger type.

Hudson Admiral, No. 7655 (highly satisfactory).

Dobbins Superbuilts, No. 133 (highly satisfactory).

Power Dusters:

DeVilbiss Hand Power Sprayer Outfit and Modified Dust Guns, for use with portable power compressor units.

The most important developments of the work in North Africa were: "(1) The demonstration, on naturally acquired infestations, that MYL and DDT are highly efficient pediculicides; (2) the development of the air-blown application of louse powder without removal of the clothing from the body of the person being deloused; (3) the demonstration that lousy people will take the trouble to come to accessible delousing stations to get relief, and (4) the development of administrative methods for the rapid disinsectization of both military and civilian populations."

<sup>54</sup> Soper, F. L., Davis, W. A., Markham, F. S., Riehl, L. A., and Buck, P.: Louse Powder Studies in North Africa (1943). Arch. Inst. Pasteur d'Algerie 23: 183-223, September 1945.

The directions for the powdering technique drawn up by Dr. Soper and his associates on 2 November 1943 were incorporated in Circular Letter No. 43, Office of the Surgeon, Headquarters, NATOUSA, 11 November 1943, subject: Typhus Fever Control. This was prepared by Colonel Stone. The statement of the procedure for insecticidal delousing became a sort of classical exposition of a portion of the prophylactic toilet of the soldier, and also of civilians. A summary of it follows.

In using the duster, powder should be distributed on the inner surfaces of inner garments and on the skin itself. The dusting of individuals should follow a routine, as follows:

1. Dust inside of the hat, dust the hair, and replace hat on head.
2. With arms extended at shoulder height at the sides, insert delivery tube up the right and then the left sleeve, and pump powder in between the skin and inner garment.
3. The delivery tube is next inserted at the back of the neck and a liberal charge of powder shot down the back.
4. The tube is next inserted inside the clothing from in front and powder sprayed first on one side, then on the chest and lastly on the other side.
5. The tube is next inserted, after the trousers are loosened, inside the innermost garment and a good dose of powder delivered to the crotch and pubic area. With the tube still in contact with the skin, the underclothing is powdered, special attention being paid to the waist and side seams.
6. With the trousers still loose, the tube is inserted down the rear of the pants next to the skin and powder is shot down over the buttocks and rear of the crotch.

The positions of dusting are shown in figure 8.

Figure 8 is a reproduction, slightly modified, of a diagram drawn by Maj. (later Lt. Col.) Theodore E. Woodward, MC, when he was training typhus control personnel in London in 1944, applying information gained in North Africa. This diagram had an almost worldwide circulation.

**The epidemic of typhus at Naples, 1943-44.**—While overrunning Sicily during July and August 1943, the Allied Forces encountered typhus, and several American soldiers came down with mild attacks of the disease. Apparently, the source of the infection was in Algeria or Tunisia.

When the Fifth U.S. Army and associated personnel entered Naples on 1 October 1943, the existence of typhus there had been indicated only by the BBC broadcast of 21 September. There appeared to be little to fear. Not a single case of typhus had been reported from Italy from 1928 until this year. The last serious outbreak before 1928 had occurred in 1919. A generation of nonimmunes had grown up, and this was the main reason for anxiety in case the disease was introduced from some source outside Italy.

Colonel Stone, Chief Preventive Medicine Officer, NATOUSA, had foreseen the possibility of an outbreak of typhus in Italy, and as noted above, had prepared to meet it. In the instance of the outbreak of typhus at Naples, he

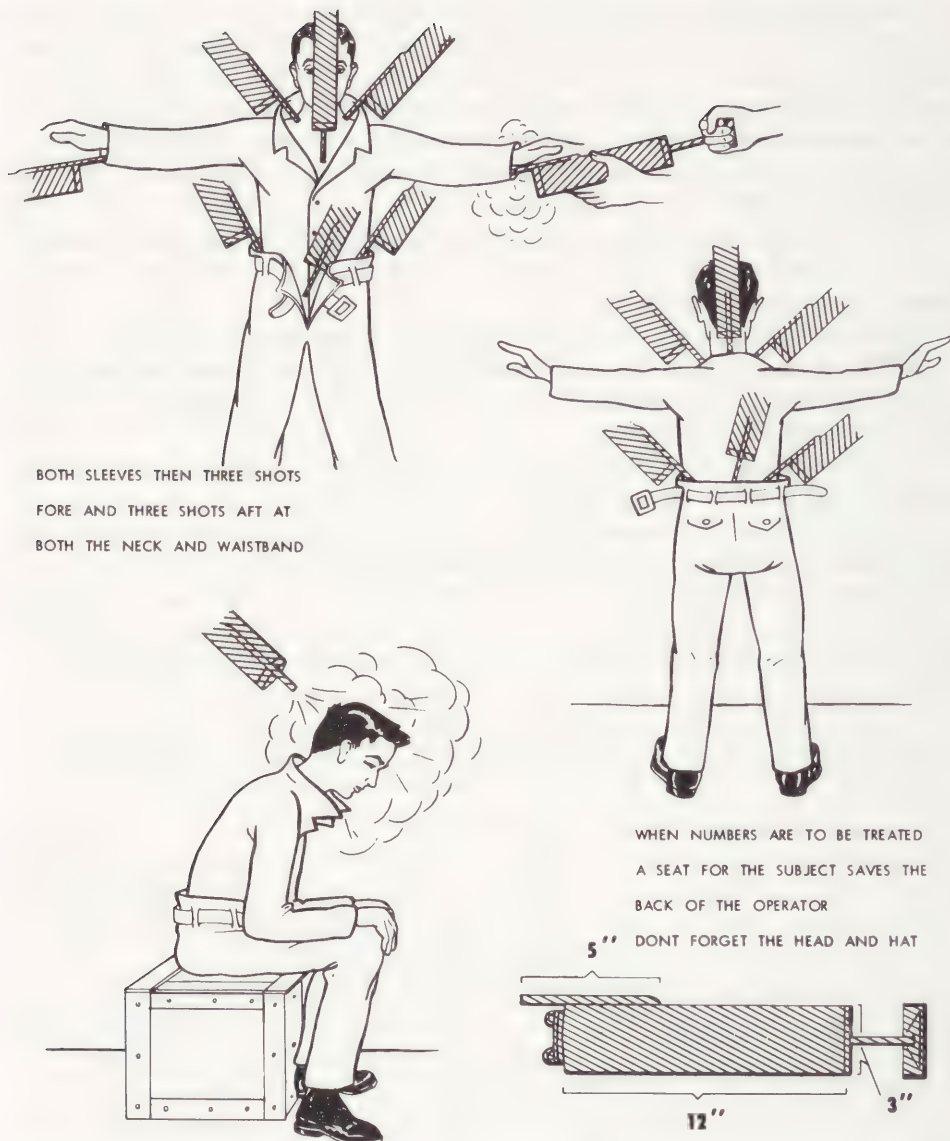


FIGURE 8.—Instructional diagram showing positions for application of louse powder with hand-operated dust gun to individual fully clothed.

found the U.S.A. Typhus Commission to be delinquent and criticized it severely.<sup>55</sup>

Apparently the disease was introduced into the mainland of Italy in February 1943 when a hospital train from the Russian front brought to Foggia

<sup>55</sup> Letter, Col. William S. Stone, MC, Preventive Medicine Officer, Headquarters, Mediterranean Theater of Operations, to The Surgeon General, U.S. Army, attn: Brig. Gen. S. Bayne-Jones, 30 July 1945, subject: Typhus Control, inclosures (36) thereto.



Italian soldiers sick with typhus fever. The first cases in Naples were reported in March 1943 in the military hospital. The first civilian case occurred at Aversa, 8 miles from Naples. Yugoslav and other Balkan prisoners of war were a major source of infection after they were liberated from the Poggioreale Prison in the industrial area of Naples.

A variable number of cases occurred from April through October. When a sharp rise took place about 7 November, it was realized that an epidemic was in the making. On 4 December 1943, Radiogram No. 9634, from Headquarters, NATOUSA, to the War Department, stated: "Typhus fever is an actual threat to military personnel in occupied Italy at this time."

Although Colonel Stone had sized up the situation on his first visit to Naples early in October 1943 and had regarded an epidemic of typhus as a probability, higher American and British authorities in AFHQ were not convinced that the danger was serious during October and the first half of November. AMGOT (Allied Military Government of Occupied Territory) and its related Allied Control Commission with a Public Health Subcommittee were not greatly concerned at this time.

Early in December, assistance proffered by the U.S.A. Typhus Commission was declined, and on 9 December, the Chief Surgeon, NATOUSA, in radio message AMSME 1664 to the Field Director of the U.S.A. Typhus Commission at Cairo, who was about to go to Naples, stated: "Forty-nine civilian cases of typhus have occurred during November in the Naples area, but actually the typhus situation is not critical in Italy."

Meanwhile, other significant events occurred, among which were:

1. *The surrender of Italy.*—Mussolini resigned on 25 July 1943, and the Italian Government surrendered on 8 September. Thereafter, the contest was with the German Army under Field Marshal Albert Kesselring—a bitter fight lasting until 5 May 1945. The Fifth U.S. Army was faced by a tough enemy who at Naples added soil for typhus by herding together there thousands of natives and refugees.

2. *Acceleration of DDT production in the United States.*—For a detailed account of the problems and accomplishments in the production of DDT in the United States, the reader is referred to Colonel Hardenbergh's chapter on insect and rodent control.<sup>56</sup> With a DDT Committee centered in the Preventive Medicine Service, under the chairmanship of Colonel Lundeborg, The Surgeon General pressed vigorously for the creation and expansion of manufacturing facilities for the production of DDT. The American and British demands for it were enormous for the control of malaria and typhus, and for many other purposes. Although production amounted to 40,000 pounds per month in September 1943 and was expected to reach 115,000 pounds per month by November, requirements greatly exceeded supply.

DDT was in such short supply in the early fall of 1943 that the War Department disapproved the urgent requisitions for it that had been placed

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<sup>56</sup> See footnote 20 (2), p. 190.

by Colonel Stone through Headquarters, NATOUSA. On 1 December, however, this point of view was changed by the intermediation of the Director of the U.S.A. Typhus Commission<sup>57</sup> and by subsequent messages to The Quartermaster General from Maj. Gen. Brehon B. Somervell and General Lutes from Cairo, about 5 December. A large supply of pure DDT and 10 percent DDT in pyrophyllite powder in 10-pound cans was moved by fast ship and airplane to Naples late in December. After its arrival there, about 26 December, it supplanted MYL which had been used for dusting up to that time, with occasional use of small amounts of DDT.

3. *London and British Typhus Commission.*—The Director of the U.S.A. Typhus Commission was in London, England, from 9 to 19 November 1943, conferring with British medical officers and civilians concerned with typhus control. Together with the Field Director (General Fox) and Major Snyder, the Director (Colonel Bayne-Jones) attended a meeting of the newly formed British Typhus Commission. As a consequence of incorrect inferences drawn by a member of the British Supply Mission in Washington, a plan had been developed by the British Ministry of Supply for the combination of the British Typhus Commission with the U.S.A. Typhus Commission to form a Joint Typhus Commission "on a high level." As neither Commission desired such an arrangement, the suggestion was not adopted. Relations between the two Commissions were cordial and mutually helpful.

4. *Conference at Algiers.*—On 20 November 1943, General Fox and Major Snyder conferred with Colonel Stone and Col. Perrin R. Long, MC, and others, at the Office of the Surgeon, Headquarters, NATOUSA, at Algiers. There are contradictory reports of what transpired at this conference. Apparently, the NATOUSA medical officers presented information about the typhus situation in Italy and the steps being taken to cope with it. These were said to have been "approved." Apparently, the U.S.A. Typhus Commission was not requested to move into the theater and did not offer to do so.

5. *The Cairo Conference.*—The developments with respect to the control of typhus in the Middle East which occurred at the first Cairo Conference from 22 to 26 November 1943 have been summarized. One aspect calls for additional emphasis. The President of the United States became directly interested in typhus, and the presence there of the Commanding General, ASF, and his Assistant Chief of Staff for Operations brought a portion of the high command of the War Department into contact with the situation and problems of a developing epidemic that was a threat to military operations. Their understanding of the extraordinary measures required to combat the outbreak was thereby enlarged.

The next important move for the control of typhus in southern Italy was the transfer of the Rockefeller Foundation Health Commission Team from Algiers to Naples. This was done on the recommendation of Colonel Stone. Drs. Soper and Davis arrived in Naples on 8 December 1943; Drs. Markham

<sup>57</sup> Minutes of Conference, Office of the Quartermaster General, Washington, D.C., 1 Dec. 1943, subject: Requisitions Received in New York Port for DDT Louse Powder.



and Riehl arrived on 10 and 17 December, respectively. The group was attached to the 2675th Regiment, Public Health and Welfare Division, Allied Control Commission, Region III.

Conditions in Naples were favorable to the development of an epidemic of typhus introduced from the outside into the nonimmune population. It was estimated that the population of the city in December 1943 was between 750,000 and 1 million. In addition, there were hundreds of Allied soldiers, returning Italians, and refugees. Living conditions were unsanitary. Food was scarce and the people were undernourished. Water, soap, electricity, fuel, and transportation were all lacking. The people were frightened, confused, and without leaders. The city was partly in rubble from bombings. People crowded not only in the still-standing multistoried dwellings but especially in the air raid shelters called "ricoveri"—large underground chambers which were mostly old tufa quarries (fig. 9) and in tunnels such as the "Tunnel of the 9th of May." Nearly all these people were lousy, and many had typhus which was transmitted to their companions in distress.<sup>58</sup>

After a conference between General Lutes and General Fox in Cairo, Major Snyder and Commander Yeomans of the Field Headquarters of the U.S.A. Typhus Commission were sent to Naples as clinical and laboratory



FIGURE 9.—View of entrances to "ricoveri" in tufa quarries at Naples, Italy, October 1943. These were crowded with homeless people, louse-infested, and afflicted with typhus.

<sup>58</sup> Wheeler, C. M.: Control of Typhus in Italy 1943-44 by Use of DDT. *Am. J. Pub. Health* 36: 119-129, February 1946.



consultants on 5 December. After remaining there about a week, they returned to Cairo and reported that a serious epidemic was in the making and that further assistance from them was not desired by the Public Health Officer (British) of AMGOT, Region III, 15th Army Group.

The epidemic increased gradually during November, rose sharply during December, and began to decline rapidly at about the end of the year. The recorded cases of typhus in Naples and its vicinity from July 1943 through May 1944 numbered 2,009. Of these, 1,403 among civilians in Naples and 500 among civilians outside of Naples, making a total of 1,903, constitute the basic figures of the epidemic. These together with certain additional cases are classified in table 35.

TABLE 35.—*Cases of and deaths due to typhus, by classification, in Naples and vicinity, July 1943 through May 1944*

Classification	Number of cases	Number of deaths	Case fatality ratio (percent)
Civilian cases in Naples.....	1, 403	318	22. 7
Civilian cases outside Naples.....	500	82	16. 4
Italian military personnel.....	23	3	13. 0
Italian civilian prisoners.....	37	11	29. 7
Unverified civilian cases.....	46	15	32. 6
Total.....	2, 009	429	21. 4

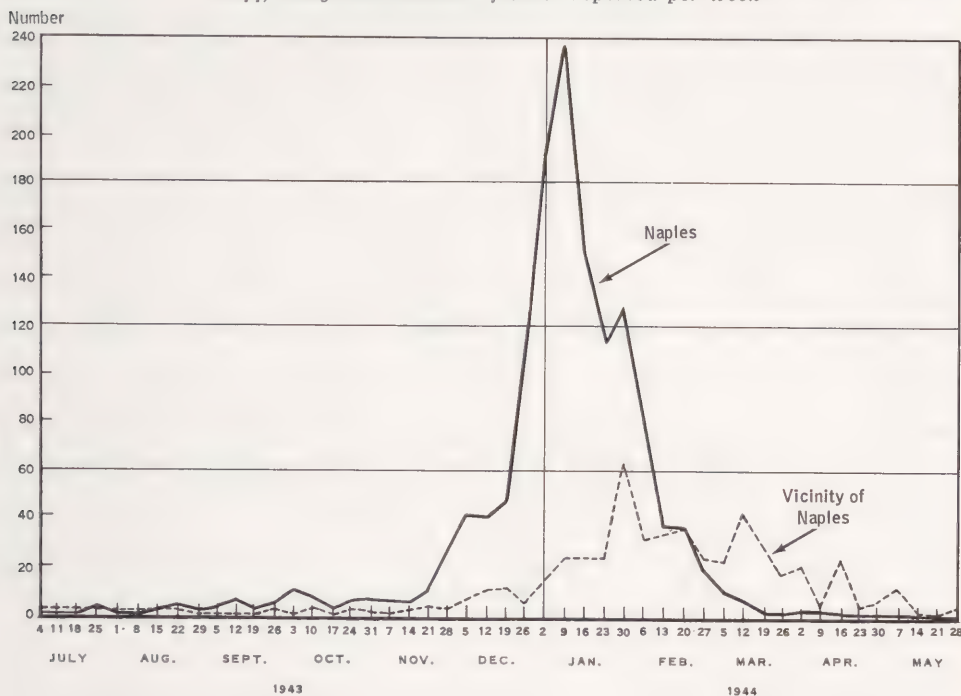
Statistics of the distribution of typhus cases among civilians in Naples and vicinity by weeks, from July 1943 through May 1944, are presented in table 36. The course of the epidemic is shown in chart 11.

As will be seen by inspection of table 36, the number of cases recorded by "onset-date" are different from the numbers as reported in the same weeks. Soper, Davis, Markham, and Riehl,<sup>59</sup> from whose publication these data have been copied, presented the figures both by onset and by report. For their graph of the epidemic, however, and for a number of important correlations and conclusions, they used the data of "onset-date." The date of onset used by them was about 8 days earlier than the report of the case. The effect of this is to change the shape of the epidemic curve and to set the main points on it back about 8 days. They used the onset data also for computation of "epidemic potential," which they define as the period of infectiousness of a typhus patient. They state:

In view of the intermediate character of the period of potential transmission, it was necessary to make an arbitrary assumption regarding its length, and it was decided to define this period as one of 18 days following onset unless in the meantime the patient had died, or had been dusted or isolated.

<sup>59</sup> Soper, F. L., Davis, W. A., Markham, F. S., and Riehl, L. A: Typhus Fever in Italy, 1943-45, and Its Control With Louse Powder. *Am. J. Hyg.* 45: 305-334, May 1947.

CHART 11.—Course of the epidemic of typhus in Naples and vicinity from July 1943 to May 1944, using the numbers of cases reported per week



Admitting that there are uncertainties introduced by these arbitrary assumptions, data based on onset-date are useful for retrospective analysis. They are of little use, however, for day-to-day decisions. Actions must be based upon reports in the first instance. In a situation as dangerous as the one at Naples, moves to counter the spread of an epidemic cannot wait upon the slow gathering of historical details. Actually, actions taken for the control of typhus at Naples were based upon current reports of cases. "The median date of onset for 1,403 cases in Naples was December 29th and that of reporting January 6th, giving an average lag of about 8 days. According to the two systems, these were the dates of the peaks.

The epidemic phase was over by 5-9 February 1944.

The disease had all the features of classical exanthematic typhus, from petechial rash to gangrene. The strains of organisms isolated from the blood of patients were identified as *R. prowazeki*. The Weil-Felix reactions with *Proteus* OX-19 were positive in titers of 1-200 or above, and specific agglutination reactions with suspensions of *R. prowazeki* were obtained. The overall case fatality rate among civilians in Naples was 22.6 percent. Mortality was related to age in the usual manner. Less than 5 percent of those under 12, and over 40 percent of those over 40 years of age, died. Although louse-borne typhus is essentially a contact disease, only 1,089 of the 1,903 patients came from households having more than one case. This was attributed to the

TABLE 36.—*Distribution of typhus cases among civilians in Naples and vicinity, by weeks, July 1943 through May 1944*

Week ending—		Naples		Outside Naples		Total	
		Onset	Reported	Onset	Reported	Onset	Reported
<i>1943</i>							
July	4	0	0	0	0	0	0
	11	1	0	0	0	1	0
	18	2	0	0	0	2	0
	25	1	3	1	0	2	3
Aug.	1	0	1	0	1	0	2
	8	2	0	2	0	4	0
	15	3	2	1	1	4	3
	22	1	3	0	2	1	5
	29	4	1	0	0	4	1
Sept.	5	5	3	0	0	5	3
	12	6	8	1	0	7	8
	19	8	4	1	0	9	4
	26	11	7	0	2	11	9
Oct.	3	8	11	1	0	9	11
	10	3	8	0	1	3	9
	17	8	3	2	0	10	3
	24	6	6	1	2	7	8
	31	1	6	0	1	1	7
Nov.	7	9	5	2	0	11	5
	14	12	5	3	2	15	7
	21	32	12	5	3	37	15
	28	46	26	6	3	52	29
Dec.	5	40	42	11	7	51	49
	12	64	42	7	9	71	51
	19	129	48	8	11	137	59
	26	224	115	21	4	245	119
<i>1944</i>							
Jan.	2	189	199	18	11	207	210
	9	137	237	23	24	160	261
	16	143	153	35	18	178	171
	23	117	116	57	25	174	141
	30	64	130	31	63	95	193
Feb.	6	43	75	37	32	80	107
	13	33	38	35	34	68	72
	20	16	38	28	37	44	75
	27	9	20	26	24	35	44
Mar.	5	10	12	38	22	48	34
	12	5	9	17	42	22	51
	19	1	3	17	32	18	35
	26	3	2	13	18	16	20
Apr.	2	4	3	16	21	20	24
	9	2	4	9	2	11	6
	16	0	1	10	21	10	22
	23	1	0	10	3	11	3
	30	0	2	4	5	4	7



TABLE 36.—*Distribution of typhus cases among civilians in Naples and vicinity, by weeks, July 1943 through May 1944—Continued*

Week ending—		Naples		Outside Naples		Total	
		Onset	Reported	Onset	Reported	Onset	Reported
1944							
May 7	-----	0	0	2	11	2	11
14	-----	0	0	0	3	0	3
21	-----	0	0	1	0	1	0
28	-----	0	0	0	3	0	3
Total	-----	1, 403	1, 403	500	500	1, 903	1, 903

breakup and scattering of families, to failures in reporting, and to the possibility that the application of louse powder to persons in the incubation period may have prevented the spread of the disease within the family. Chemotherapeutic studies by the British Typhus Team under Col. C. H. Stuart-Harris, R.A.M.C., and Maj. M. van den Ende, R.A.M.C., led to the opinion that neither benzamine drugs (V-147 and V-186) nor PABA were of any value in the treatment of typhus.

At the start of the epidemic in October 1943 and well into December, the guiding and controlling medical authority with respect to typhus in relation to U.S. Army troops in Naples and southern Italy was the Office of the Chief Surgeon, Headquarters, NATOUSA, where Colonel Stone was Chief Preventive Medicine Officer. The activities of his office were coordinated with those of AFHQ regarding medical, public health, and civil affairs, with AMGOT, and with the Allied Control Commission.

The Rockefeller Foundation Health Commission Team, transferred from Algiers to Naples on 8-15 December, attempted at once to institute measures for the control of the epidemic. This team initiated a program for typhus control based upon older principles modified by the team's own development of the use of louse powder and procedures devised in North Africa. It was able to start contact delousing with MYL, and some DDT, louse powders on 15 December 1943. It might have been foreseen, however, that a civilian group could not function effectively in an active zone of military combat. Insurmountable and frustrating administrative and logistic difficulties occurred.

An example of hand-operated dusting with louse powder is shown in figure 10.

On 20 December 1943, when General Fox, Field Director of the U.S.A. Typhus Commission arrived in Naples in response to an invitation, an important conference was held with General Hughes, the British Deputy Commander of NATOUSA, Maj. Gen. Arthur W. Pence, commanding the Peninsular Base Section, Colonel Stone, and others. Out of this came the



FIGURE 10.—Italian woman using hand-operated dust gun to apply louse powder underneath the shirt sleeve of a boy, Naples, 1943.

decision to request the War Department to place the U.S.A. Typhus Commission in charge of typhus control at Naples. Agreement was reached upon arrangements for the provision of American and British personnel for the work, and for the furnishing of transport from U.S. Army units in the vicinity. Naples was declared "out of bounds" for Allied soldiers. On this date (20 Dec. 1943), the U.S.A. Typhus Commission, although not yet formally in control, became a directing agency. On 3 January 1944, the Commission was put in charge of typhus control at Naples. Thereafter, additional personnel was obtained from British and American military units in the area, and from a special shipment of Italian-speaking U.S. Army medical officers made through the Office of The Surgeon General in Washington. General Fox remained in Naples until 9 January 1944, when he returned to Washington for conferences. On conclusion of business there, he returned to Naples on 2 February.

Of great importance to the U.S.A. Typhus Commission and for effective command was the assignment of Col. Harry A. Bishop, MC, as a "deputy" of the Field Director at Naples from 28 December 1943 to 16 February 1944. His report<sup>60</sup> is full of valuable information.

<sup>60</sup> Report, Col. Harry A. Bishop, MC, United States of America Typhus Commission, for the Field Director, United States of America Typhus Commission, 16 Feb. 1944, on the Control of Typhus Fever in Naples and Southern Italy, from 28 Dec. 1943 to 16 Feb. 1944.

On 9 January 1944, U.S. Navy Epidemiology Unit No. 23 (Lt. H. M. Gezon, MC, USNR, commanding) arrived at Naples and participated in the work of typhus control until 7 February 1944.<sup>61</sup>

The Allied armies in Italy formed a Typhus Control Board on 11 January 1944, but it exerted little or no influence. Within less than a month, during the period 5-9 February 1944, the epidemic was judged to be under control, and on 20 February, the Allied Control Commission took over typhus control work among the civil population of Italy,<sup>62</sup> and the U.S.A. Typhus Commission withdrew. In connection with this, Brigadier Galloway wrote:<sup>63</sup>

1. The responsibility for the organization of civilian antityphus measures in Italy, previously undertaken by the U.S.A. Typhus Commission, was assumed by the Director of Public Health Sub-Commission, Allied Control Commission, at 2359 hours, 19 February 1944.

2. It is desired to place on record the invaluable work carried out by the U.S.A. Typhus Commission under the control of Brig. Gen. Leon A. Fox and directed by Col. Harry A. Bishop. As a result of the energetic measures put into operation, the number of cases rapidly diminished and the epidemic was brought under control. The advice and assistance given by the Commission was a most important factor in bringing about an effective and harmonious coordination of military and civil preventive measures.

**Control measures.**—The control measures which so promptly subdued the epidemic of typhus in Naples were numerous and varied, frontal and flanking. They were not all of equal importance, but each contributed something to the success. These measures may be grouped as follows:

1. Case finding, isolation, and removal of patients to hospitals.
2. Delousing with louse powders:
  - a. Contact delousing.
  - b. Block delousing.
  - c. Air-raid shelter delousing.
  - d. Institutional delousing.
  - e. Military and military labor delousing.
  - f. Refugee delousing.
  - g. Mass delousing.
3. Immunization with typhus vaccine.
4. Training of personnel for typhus control.
5. Publicity and education.
6. "Flying Squadron" to deal with cases and situations in outlying districts or villages.

Of these control measures, the two that were of greatest importance at Naples were case finding, followed by isolation of patients in hospitals, and

<sup>61</sup> Report, Lt. H. M. Gezon, MC, USNR, Commanding U.S. Navy Epidemiology Unit No. 23, for Chief, Bureau of Medicine and Surgery, U.S. Navy, via Commander, U.S. Naval Forces, Northwest African Waters, 27 Feb. 1944, subject: Typhus Fever Epidemic, Naples, Italy, 1943-44.

<sup>62</sup> Report, Lt. Col. Wilson C. Williams, MC, to the Regional Public Health Officer, Region III, Allied Control Commission, Naples, Italy, 1 June 1944, subject: Typhus Fever in Naples and Occupied Italy.

<sup>63</sup> Letter, Brigadier Galloway, D.D.M.S., Allied Force Headquarters, Advance Administrative Echelon, C.M.F., to D/C.A.O., Allied Force Headquarters, Advance Administrative Echelon, 21 Feb. 1944, subject: Typhus.



contact delousing, by which a barrage of louse powder was thrown around each single focus of infection.

Mass delousing was gotten underway by about 28 December 1943. Between 31 December 1943 and 31 May 1944, a total of 3,265,786 persons (many of whom were repeaters) had been dusted with louse powder at about 40 dusting stations in Naples. The analysis by Soper and his associates<sup>64</sup> shows that the peak of the epidemic had just about passed when mass delousing began. Considered judgment attributes to contact delousing and block delousing the main deterrent to the epidemic. The delousing was accomplished by the application of louse powders, first MYL and later DDT, with hand dust guns (blowers) without removal of clothing. At Naples, mass delousing was done with hand dusters. Later in 1944, power dusters became available, one type of which is shown in figures 11 and 12.

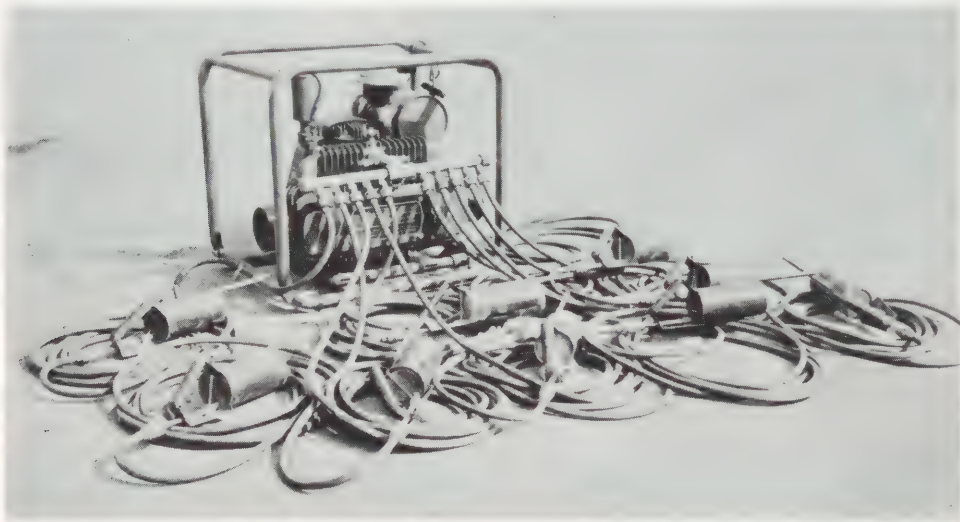


FIGURE 11.—Gasoline-motor-driven multiple applicator for dusting clothed individuals with louse powder.

Immunization with typhus vaccine was of little consequence in the direct control of the epidemic. Indirectly, it was of value in protecting expert personnel who were constantly exposed to infection.

Considerable space might be occupied by the logistic accounts about supplies, transport, and personnel. While the records are not complete, they are full of details. The cited reports of Colonel Bishop and Colonel Williams are the best sources of such logistic information.<sup>65</sup> A few of the records are summarized here, as follows:

1. Control sections, or services, usually consisted of 1 to 8 officers and 6 to 40 civilians.

<sup>64</sup> See footnote 59, p. 222.

<sup>65</sup> See footnotes 60, p. 226; and 62, p. 227.



FIGURE 12.—Motor-driven duster in operation.

2. At the peak of the epidemic in Naples and vicinity, the group under the direction of the U.S.A. Typhus Commission consisted of:

42 U.S. Medical Department officers, including 6 Italian-speaking officers

4 R.A.M.C. officers

15 Italian doctors

3 Italian-American doctors, civilian employees

600 civilians, mostly employed as dusters

In addition, there was a considerable body of military personnel, such as drivers, messengers, and so forth, supplied by the Fifth U.S. Army and the Peninsular Base Section.

Many things, some complimentary and some derogatory, have been written and said about the Army's experience with typhus at Naples in 1943-44. On the whole, the record was excellent and the accomplishment was large enough to afford credit to all organizations and individuals that participated in the achievement. Quotations from publications of British colleagues well express the favorable ending. For example, in 1946, Col. H. D. Chalke, R.A.M.C.,

who was the Public Health Officer, Allied Control Commission, wrote:<sup>66</sup>

The fight against the epidemic has been called the second battle of Naples, and undoubtedly, had it not been won, the Allied cause may well have been seriously endangered. Tribute must be paid to all who took part in the battle—the members of the U.S.A. Typhus Commission, the Rockefeller Foundation workers, A.M.G. and British and American Medical Services personnel, all of whom worked untiringly in full cooperation and harmony.

The former Director of the U.S.A. Typhus Commission, author of this chapter, sadly wishes that the kind estimate of Colonel Chalke with regard to harmonious collaboration had been true for the American units and personalities. Actually, he has rarely been involved in a more troublesome and acrimonious controversy than the one that arose over disputes concerning who did what and when in the counterattack on typhus at Naples. This reached such a pitch that the British became involved in it, suggesting that it might be advisable to attempt to reach an "international settlement" of the questions. To this end, on 6 January 1944, the Director of the U.S.A. Typhus Commission obtained approval for the establishment in the Office of the Chief, Civil Affairs Division, War Department Special Staff, of an ad hoc Committee on Typhus Control Report.<sup>67</sup>

It was hoped that matters in dispute might be adjudicated by such a committee, with a view to the issuance of a joint American and British report. The ensuing conferences and correspondence became quite as involved as one might have expected from experience with any attempt to harmonize international differences that were intensified by intranational disagreements. By the end of January 1946, it was realized that the attempt was futile, and the matter of a Joint Naples Typhus Report was dropped.

Of the significance of the experience at Naples, Colonel Chalke wrote:

Naples taught us that an army can live and work in an overcrowded, war-damaged, typhus-ridden city, provided adequate precautions are taken \* \* \*. It showed us the benefits of mechanical methods of using insecticides on fully clothed subjects, and enabled the cumbersome steam and hot air disinfestors which took up so much transport, to be dispensed with. It also showed beyond question that DDT was a new weapon of tremendous possibilities.

In his foreword to a report of the Allied Control Commission for Italy in 1945, Brig. G. S. Parkinson, R.A.M.C., Director, Public Health Section, wrote:

The conclusions to be drawn from the "experiment" [at Naples] are clearcut and inescapable. It is now possible to control epidemic typhus even in a large densely populated and heavily infested urban community under wartime conditions.

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<sup>66</sup> Chalke, H. D.: DDT. Experiences of Its Use During the Italian Campaign. *Proc. Roy. Soc. Med.* 39: 165-168, 1946.

<sup>67</sup> (1) Letter, Brig. Gen. S. Bayne-Jones, Director, United States of America Typhus Commission, to Maj. Gen. John H. Hildring, Director, Civil Affairs Division, War Department, 23 Jan. 1945, subject: Proposal for Combined Anglo-American Report on the Outbreak and Control of Typhus Fever in Naples and Southern Italy, 1943-44. (2) Letter, Brig. Gen. S. Bayne-Jones, Chairman, Technical Report Committee, to Steering Committee on Combined Report on the Outbreak of Typhus Fever in Naples and Southern Italy, 1943-44, Combined Civil Affairs Committee, 8 Oct. 1945, subject: Status Report and Recommendation.



The typhus epidemic at Naples will doubtless stand out as a milestone in the field of public health and disease control. Here it was for the first time that a major epidemic of this vicious disease, which characteristically strikes men when they are down, was not merely curbed but actually brought under control by the vigorous application of delousing measures. The significance of this fact for \* \* \* the inhabitants of the old endemic centers of typhus is inestimable. It may be a long time before it can be said that typhus has been eliminated as a primary public health problem, but that event need no longer be delayed for want of an efficient means of controlling the disease.

The statistics of typhus in Naples and vicinity from July 1943 through May 1944, including weekly records of cases by report and by onset, are presented in table 36. These data, on the basis of reported cases, are shown graphically in chart 11.

**Typhus control in the Fifth U.S. Army.**—The Fifth U.S. Army not only contributed personnel and transport to assist in the counterattack upon the typhus epidemic in Naples in 1943–44 but also maintained effective typhus control measures within its own units. The following is quoted from the “History of the Fifth Army Medical Service, 1945,” page 104:

When Fifth Army troops prepared for the invasion of Italy in 1943, each soldier had available a 2-ounce can of “Insecticide Powder for Body Crawling Insects.” Troops were thoroughly familiar with its use and their frequent and free use of the powder, both on their bodies and in their bedding, indicated its popularity. Although the powder was MYL and not DDT, the results obtained from its frequent use were effective. No increase in body louse infestations among troops was noted.

In November 1943, typhus fever was recognized among civilians in Naples and an intensive educational program relating to typhus control was begun in the Fifth Army. Demonstration teams were organized from the 28th Malaria Control Detachment and meetings were held with the Divisions at which all preventive and control measures for body lice were explained. On 1 January 1944, a detail of seven enlisted men and one officer from the 28th Malaria Control Detachment was sent to Naples to arrange for the dusting with insecticide powder of all Army troops on their arrival and departure at the Fifth Army Rest Camps. With the further increase of cases of typhus fever in Naples, the city was placed off-limits and the rest camps closed. The effectiveness of this program was shown by a decline in reported body louse cases from 219 in December 1943 to 35 in March 1944. Only one case of suspected typhus occurred in Fifth Army troops, and this diagnosis was never confirmed.

On 1 October 1944, a new educational program was inaugurated and meetings were again held with all Divisions and with Army troops. These meetings were attended by regimental and battalion medical officers and by selected enlisted personnel. Demonstrations were given of improved hand dust gun methods of spreading DDT powder which was now available for body louse control. An important part of the louse control program was the work of the Quartermaster Bath and Sterilization Detachments, the services of which were available to every unit of the Fifth Army.

This campaign against body lice was so successful that despite the fact that units were required to report cases of lice, from October 1944 through March 1945, only 32 cases of lice were reported.

At the conclusion of hostilities in May 1945, the Fifth Army Surgeon supervised the dusting with DDT powder of all German prisoners of war and surrendered German troops held by Fifth Army. The dusting was carried out by German medical corpsmen trained and supervised by American Army personnel, and became a routine part of the prisoner-of-war processing.

## EPIDEMIC TYPHUS IN EUROPEAN REGIONS, 1943-46

## The European Theater of Operations, 1943-45

In this chapter, the account of preparations for the control of typhus in the European Theater of Operations was broken off on 7-8 November 1942 on the eve of the invasion of North Africa. Having followed the campaigns and activities in the Mediterranean area and in the Middle East to their terminations, the narrative now returns, on 1 January 1943, to plans and actions going forward in England, the great base for mounting the invasion of Europe.

With special respect to epidemic typhus and its control, the account of activities in this theater will be concerned primarily with the mounting of Operation OVERLORD (the invasion of Europe), events following the landing in Normandy on D-day, 6 June 1944, the encounter with typhus in the Rhineland in 1945, the tremendous problems of civil public health in relation to typhus extending well beyond the end of the military phase of the campaign, the closing of ETOUSA on 1 July 1945, and to the end of April 1946 when the last representative of the U.S.A. Typhus Commission was withdrawn from USFET.

In England in January 1943, Colonel Gordon (p. 198), was building up his organization to provide the best possible preventive medical service to ground troops of the U.S. Army in the British Isles. As Colonel Gordon has written in his historical reports,<sup>68</sup> from which much of the material for this section is drawn, that there was at this time "scant idea of what the future held." Soon, however, rumors having their origin in the Casablanca Conference on 14 January 1943, when the Combined Chiefs of Staff first decided that plans should be made for a cross-Channel invasion in 1944, alerted all wise planners. It was not until 17 August 1943 that the plans were approved at the first Quebec Conference. At the second Cairo Conference, 3-7 December 1943, these plans were made more definite when Gen. Dwight D. Eisenhower was selected as Supreme Allied Commander for Operation OVERLORD. These decisions had been wisely anticipated by the Preventive Medicine Division of the European theater and plans had been formulated accordingly.

In January 1943, the strength of U.S. Army troops in the "European Command" in the British Isles was 120,000. In January 1944, it was 935,000. On D-day, 6 June 1944, the strength was more than 1.5 million. The U.S. Army Forces were increased continuously during the victorious advance through France, Holland, and Germany, reaching a maximum of 3,060,000 in April 1945. After the surrender of Germany, on 8 May 1945, the strength of ETOUSA

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<sup>68</sup>(1) Gordon, John E.: A History of Preventive Medicine in the European Theater of Operations, U.S. Army, 1941-45, vol. I, pt. I, pp. 1-43, and pt. III, pp. 1-54, with tables and illustrations. [Official record.] (2) Gordon, John E.: Louseborne Typhus Fever in the European Theater of Operations, U.S. Army, 1945. In *Rickettsial Diseases of Man*. Washington: American Association for the Advancement of Science, 1948, pp. 16-27.

and its successor USFET was rapidly reduced through deployment to the Pacific and demobilization. On 31 December 1945, the strength was down to 666,000 and to 326,000 on 30 June 1946.

During the whole period, as shown in table 33, there were only 10 cases of epidemic typhus, and no deaths from the disease, among U.S. Army personnel in ETOUSA. There were no cases until 1945, when 10 occurred among troops in the Rhineland where the exposure was relatively intense.

Medical intelligence indicated that typhus was occurring in the German Reich and would be encountered by U.S. Army Forces when they entered that country. The disease was introduced from Russia and Poland in 1939. In 1942 and 1943, 2,742 and 3,316 cases were reported, respectively, and it has been estimated that there were at least 5,058 cases of typhus in Germany during 1943. In the Rhineland, there were 250 cases reported in 1942, and 350 in 1943.

Although epidemic typhus was occurring among German troops, particularly on the Eastern front, and among Polish and Russian prisoners of war in detention camps and at places where they were used as laborers, the chief incidence of the disease was among civilians—mainly displaced persons and victims of oppression in the ghastly concentration camps such as Dachau and Belsen. It was occurring also among German civilians in bombed towns and cities.

Colonel Gordon has noted:

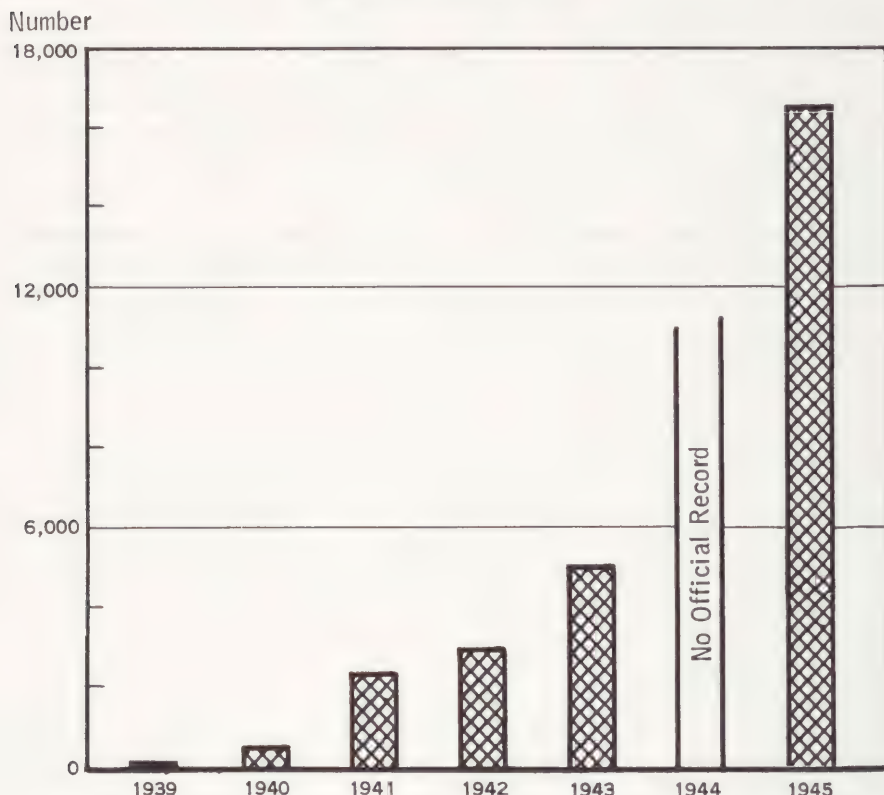
Typhus spread to all principal regions of Germany and became epidemic in some areas. Considering the frequency with which new infections were introduced, control measures would appear to have been good, in that typhus was held to reasonably low levels. The final debacle of the war led to conditions marked by disorganization and great shifts of population of such extent that the epidemic potential was extremely dangerous when American troops entered the country.

Although there are no official German records for 1944, it is known that the incidence of typhus increased significantly in the area later to be known as the U.S. Occupied Zone of Germany during that year. From January to June 1945, there was a great increase to 16,506 cases, and it was estimated that approximately 22,000 cases of typhus occurred in the U.S. Occupied Zone of Germany during the year 1945. Colonel Gordon's graph of these statistics is reproduced in chart 12, showing the number of reported cases of typhus fever in Germany and annexed territory by years from January 1939 to June 1945, with the 1945 data limited to the U.S. Occupied Zone.

During 1943 and the first 5 months of 1944, the typhus control activities of the Preventive Medicine Division of the Office of the Chief Surgeon, ETOUSA, and of the U.S.A. Typhus Commission (p. 236) in England were devoted almost entirely to education, training, development of methods, and stockpiling of equipment and supplies. The program of the U.S. Army for typhus control in Europe may be summarized under six major headings derived



CHART 12.—*Reported cases of typhus fever in Germany and annexed territory by years, January 1939–June 1945\**



\*The data for the first 6 months of 1945 relate only to the U.S. Occupied Zone.

Source: Gordon, John E.: *Louseborne Typhus Fever in the European Theater of Operations*, U.S. Army, 1945. *In* *Rickettsial Diseases of Man*. Washington: American Association for the Advancement of Science, 1948.

from the principles set forth by the Committee of Experts in 1937 (p. 184) and experience gained at Naples in 1943–44, as follows:

1. An adequate system of reporting cases of typhus in all population groups involved, both military and civilian.
2. A system of case finding, providing for prompt discovery of new cases and newly developing foci of infection.
3. Isolation and hospitalization of patients with typhus fever.
4. Quarantine of highly infected areas or camps, and the institution of a cordon sanitaire to protect larger districts relatively free from typhus from infection carried from areas of high endemicity or epidemic prevalence.
5. Delousing of patients, contacts, and at times large groups (in infected towns and camps) by the use of DDT louse powder. Delousing was regarded as the core of the typhus control program, "the one reliance above all others."

6. Immunization with typhus vaccine of all military personnel, all essential civilians, and occasionally larger groups of civilians such as inmates of concentration camps.

During this preparatory period before the landings in Normandy, two organizational and administrative developments occurred which greatly strengthened the typhus control activities in ETOUSA. These were:

1. The establishment of a Civil Public Health Division first in Headquarters, ETOUSA, and later, in 1943, in the Office of the Chief of Staff of the Supreme Allied Commander. Somewhat later, this Civil Public Health Division was placed under Assistant Chief of Staff, G-5, SHAEF.

2. The establishment of the London Field Headquarters of the United States of America Typhus Commission in direct relationship with G-5, SHAEF, on 17 May 1944.

As epidemic typhus was primarily a civilian pestilence which threatened the military, a summary of some of the arrangements for dealing with civil affairs is presented at this point to provide a basis for the understanding of subsequent actions.

### *Civil public health in occupied and liberated countries*

In early 1940, Colonel Simmons (p. 184) foresaw that problems and activities of civil public health in relation to military government of occupied and liberated countries would be vast and complicated if the United States should become involved in the European war with its inevitable global extension. He initiated studies and actions that contributed greatly to the development of the program for civil public health under military jurisdiction overseas. From the beginning and throughout the war, he was aided especially by Lt. Col. (later Col.) Ira V. Hiscock, SnC, who from 1941 to 1945 was in effect the representative of The Surgeon General on the staff of Maj. Gen. John H. Hilldring, GS, Chief of the Division of Civil Affairs and Military Government, of the War Department Special Staff. In 1943, Lt. Col. (later Col.) Thomas B. Turner, MC, as chief of the Civil Public Health Division in the Preventive Medicine Service, exerted a strong influence on the development of policy and upon actions. These two former officers who had so much to do with the entire program are among the chief authors of the volume in this series dealing with this important part of the history of preventive medicine in World War II.<sup>69</sup>

By the end of 1943 in ETOUSA, there were two staff sections known as G-5 which were concerned with civil affairs and military government for occupied and liberated countries. One was in Headquarters, ETOUSA, and the other in Headquarters, SHAEF. There was also a British organization for work in the same field. Although the two Allied organizations worked closely together, they had to face different tasks in their respective Army zones. Their stories are different. This section will be concerned almost entirely with the

<sup>69</sup> Medical Department, United States Army. Preventive Medicine in World War II. Volume VIII. Civil Affairs-Military Government Public Health Activities. [In preparation.]

American organization, with special reference to the prevention and control of typhus.

By the time of the Normandy landings, early in June 1944, several reorganizations had taken place in arrangements for civil affairs. The Civil Affairs Division of G-5, SHAEF, had been given comprehensive jurisdiction. The Public Health Branch of this Division became especially important in relation to typhus control. Although Maj. Gen. Albert W. Kenner was the Chief Medical Officer of SHAEF, he was not as much concerned with typhus control as was Maj. Gen. W. F. Draper (Assistant Surgeon General of the U.S. Public Health Service, on leave) who, on the recommendation of General Simmons and Colonel Turner, had been appointed Chief of the Public Health Branch, G-5, SHAEF, on 1 May 1944. Among the members of General Draper's staff were Col. William L. Wilson, MC, and Lt. Col. (later Col.) Leonard A. Scheele, MC, who after the war succeeded Dr. Thomas Parran as Surgeon General of the U.S. Public Health Service. Both were expertly informed and had close relations with the U.S.A. Typhus Commission.

According to Colonel Gordon: "The control of typhus among civilians of liberated countries and among displaced nationals was an accepted and direct responsibility of G-5 Civil Affairs and Military Government." Prior to D-day, this Branch was not sufficiently organized or trained to meet these obligations. Training in typhus control was provided by the Preventive Medicine Division of the Office of the Chief Surgeon, ETOUSA, and by the U.S.A. Typhus Commission.

As the invasion progressed, the Public Health Branch of SHAEF headquarters prepared and issued the technical directions for typhus control among civilians and assured the provision of adequate supplies. Naturally, SHAEF had to delegate responsibility for carrying out typhus control measures in many local situations. As Colonel Gordon wrote, after giving credit to various organizations, including the U.S.A. Typhus Commission: "The innumerable surgeons of armies, corps, divisions and their staffs were directly concerned with implementing the program. They did the work of the day. To this group more than all others fell the responsibility for the necessary measures upon which satisfactory control depended." The author of this chapter wishes that there were space here to mention them individually.

#### *Establishment of Field Headquarters of the U.S.A. Typhus Commission in the European Theater of Operations*

On 27 December 1942, by letter from The Adjutant General by order of the Secretary of War, AG 710 (12-26-42) OB-S-E, the Commanding General, ETOUSA, had been notified of the establishment of the U.S.A. Typhus Commission and was furnished a copy of Executive Order No. 9285 (p. 201). The tentative plans of the Commission were outlined, including the possibility of visits to London and other places in the theater at such times as would be agreeable to the commanding general. While in ETOUSA, the members of the Commission would be under the control of the commanding general. The



communication expressed clearly the desires and authorizations for theater support of the Commission with funds, housing, subsistence, labor, technical assistance, and transportation.

On 26 February 1944, General Fox and Colonel Turner arrived in London for consultations with General Hawley, Colonel Whayne, the Assistant Military Attaché at the American Embassy, the British medical military authorities, the British Typhus Committee, the British Medical Research Council, and other individuals and organizations. As a result of these conferences, the U.S.A. Typhus Commission was accorded both advisory and certain operational functions in the European theater.

It was agreeable to General Hawley, Chief Surgeon, ETOUSA, representing the Commanding General, ETOUSA, that the U.S.A. Typhus Commission should have an office in London, and he did not insist that it should be attached to his office. Before the final decision on its attachment to SHAEF was reached, however, an interesting and somewhat delicate episode occurred. General Fox accepted the cordial invitation of the American Ambassador, John G. Winant, to house the Commission in the American Embassy, and he asked for War Department approval.<sup>70</sup> The Embassy and General Fox were informed by radiogram that there would be no objection to acceptance of quarters and facilities offered by the Embassy, but by direction of the Secretary of War, the activities of the Commission in the European theater would be under the jurisdiction of the theater commander and that General Fox would report through military channels to the Headquarters of the Commission in Washington, and not through the American Embassy in London. To this, the U.S. Military Attaché in London replied that the proposed association of the Commission with the American Embassy had been predicated upon the Commission's independent responsibility to the Secretary of War and that placing it under the jurisdiction of the Commanding General, ETOUSA, precluded formal association with the Embassy.

Finally, the U.S.A. Typhus Commission was attached to the Public Health Branch, Civil Affairs Division, G-5, SHAEF, in which connection it was a part of the organization of the theater while maintaining its integrity and scope as a miscellaneous War Department activity administered through its own headquarters in Washington and, at this time, by the Office of the Deputy Chief of Staff of the Army. On 17 May 1944, the Field Headquarters of the U.S.A. Typhus Commission in London was established at 44 Grosvenor Square, and later two refrigerated warehouses were acquired for the storage of typhus vaccine.

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<sup>70</sup>(1) Memorandums, for file and record by Brig. Gen. S. Bayne-Jones, Director, United States of America Typhus Commission, 18-28 Mar. 1944, subject: London Office of Commission in Relation to European Theater of Operations and American Embassy. (2) Memorandum, Lt. Col. Tom F. Whayne, MC, Assistant Military Attaché, American Embassy, London: 1 Grosvenor Square, 13 Mar. 1944, subject: Consultations Concerning the United States of America Typhus Commission and Public Health Section of Civil Affairs Division During the Recent Visit to London of Brig. Gen. Leon A. Fox and Col. Thomas B. Turner, MC.

During the next 2 years, from May 1944 to May 1946, the U.S.A. Typhus Commission was engaged in every major, and many a minor, episode of typhus control on the continent of Europe, from the French Channel Coast to Berlin. Only a few can be summarized here, and this will be done at the risk of violating chronology and of an apparent disregard of the activities of the Preventive Medicine Division, ETOUSA, and activities of the medical detachments of combat units.

The Presidential Executive Order No. 9285, establishing the U.S.A. Typhus Commission was a powerful instrument for securing the means for typhus control, not only through the Commission but through other military and civilian agencies with which the Commission became associated. It was helpful to Civil Affairs and to UNRRA, and to British as well as American organizations. It enabled the Commission to cooperate with other agencies in dealing with problems of typhus among civilians, refugees, displaced persons, and prisoners of war. To confirm its status to deal with typhus control in Europe, the War Department (Marshall to Eisenhower) sent Radiogram No. WAR 28982 to the Commanding General, U.S. Army Forces in the European Theater of Operations, on 26 April 1944, referring to the original letter of notification of 27 December 1942, announcing that General Fox would soon establish an office of the Commission in London, and again expressing the desire "that the Commission be furnished with all necessary support to insure proper functioning of the Commission under Executive Order No. 9285 dated 24 December 1942."

Immediately after the establishment of the Field Headquarters of the U.S.A. Typhus Commission in London in May 1944, it became engaged in training personnel of the British, the Free French, and the Netherlands Government-in-exile in the latest methods of typhus control, including lessons learned at Naples. This instruction was directed by Major Woodward whose diagram (fig. 8) of the positions of dusting DDT powder with a hand duster became a one-page manual used from Europe to the Far East. The hand dusters were the Hudson and Admiral types referred to in the section on the epidemic of typhus in Naples (p. 217). By this time, also, a power duster had been developed by the Office of the Quartermaster General in collaboration with the Headquarters of the U.S.A. Typhus Commission in Washington in the spring and summer of 1944. By September 1944, "the outfit, delousing, gasoline engine driven," QM Item No. 66-0-800E, was ready for distribution. A typical example of it is shown in figures 11 and 12. This machine, rapidly improvised, was far from perfect. It failed at times from lack of fuel or power, and the pyrophyllite in the DDT powder was so abrasive that it scored the bearings. Nevertheless, it served well in the dusting of thousands of refugees at river crossings and at railroad stations, and in concentration camps until the end of these sad affairs in 1946.

**Typhus vaccine.**—By an arrangement with the Office of the Chief Surgeon, ETOUSA, the U.S.A. Typhus Commission was put in charge of all supplies of typhus vaccine for the theater. On 1 July 1944, Lt. Col. (later



Col.) Silas B. Hays, MC,<sup>71</sup> cut through red tape and turned over to the Commission in London 100,000 vials, 20 ml. each (2 million ml.) of typhus vaccine, Medical Supply Item No. 1612800. Thereafter, the Commission stockpiled and issued typhus vaccine to U.S. Army troops, British organizations, UNRRA, and other civilian and military units concerned with typhus control in Europe. Perhaps upward of 20 million ml. of the vaccine was distributed through this system.

**DDT.**—The Field Director of the Commission desired to have DDT louse powder and DDT concentrate placed under control of the U.S.A. Typhus Commission in ETOUSA. Theater authorities did not agree with this. As a consequence, the requirements of the theater and of SHAEF were handled from their respective offices, with the constant support of the Commission. A notable example of cooperative effort was the shipment by air of 1,125,000 pounds of DDT louse powder and 7,200 hand dusters from the United States to England in September 1944 for use on the Continent. This action followed a visit to Headquarters, U.S.A. Typhus Commission, in Washington by Colonel Scheele who persuasively presented the needs of the Public Health Branch, G-5, SHAEF. The desired supply of DDT louse powder was secured promptly by the concurring action of Colonel Lundeborg, chairman of The Surgeon General's DDT Committee, the approval of The Surgeon General, Maj. Gen. Norman T. Kirk, and the authorization by Maj. Glen E. Edgerton, Director of the International Division, ASF.

**Civil Affairs Division antityphus unit.**—In the latter half of 1943, the U.S.A. Typhus Commission in Washington worked with the Supply Division, Office of The Surgeon General, in consultation with numerous advisers, on selections of items for a standard unit of materials for typhus control. The outcome was a "unit" (called CAD (Civil Affairs Division) antityphus unit) weighing 759 pounds, with a cubage of 36 cubic feet containing typhus vaccine, syringes, DDT louse powder, dusters, methyl bromide, goggles, protective clothing, thermometers, lanterns, gloves, and some miscellaneous items. Thousands of these units were shipped to the European and Mediterranean theaters, and also to Japan and Korea. In spite of some objections, they were found to be serviceable.

In discussing the supply situation, Colonel Gordon had pointed out that demands for antityphus control materials were not urgent until the advance across the Roer River in February 1945, when the full impact of the disease became manifest. He wrote:

By the time supplies were needed, ample quantities [of DDT louse powder] were available on the Continent. From an insignificant monthly demand for about 3.5 tons of DDT powder in January 1945 by G-5 of the armies, the requirements jumped to approximately 150 tons by the following April 1945 \* \* \*. The problems of supply just presented related only to intra-theater effort and concern. Particular commendation is due the Service of Preventive Medicine in the Office of The Surgeon General and the Director

<sup>71</sup> Colonel Hays later became The Surgeon General of the U.S. Army and served in that capacity from 1 June 1955 to 31 May 1959.



of the U.S.A. Typhus Commission in Washington for the diligence and effort exercised at the source of supply, which made possible long in advance of need the huge stockpiles accumulated in the United Kingdom. One of the most satisfactory features of typhus control as it developed in Germany was that never in the course of operations did a shortage of dusting powder exist.

**Prisoners of war.**—The Commission assisted in the vaccination and delousing of prisoners of war taken by American forces, and attempted to get antityphus materials to American prisoners of war held by the Germans. Although the assistance of the International Red Cross was solicited, the effort to furnish these materials for U.S. nationals imprisoned in war camps in Germany failed.

**Scientific investigations.**—Members of the U.S.A. Typhus Commission utilized every possible opportunity to make scientific investigations of typhus in various situations in Europe. Strains of the rickettsial organism, all of which proved to be *R. prowazeki*, were collected and sent to the Army Medical Service laboratories in Washington and to laboratories in England. Serum specimens were collected and distributed to various laboratories. Chemotherapeutic and clinical studies were carried out under distressing and difficult conditions at the German concentration camps, after they had been captured by U.S. troops.

**Personnel.**—Thus far, a number of names have been mentioned to memorialize those on the staffs of ETOUSA and SHAEF who served the cause of typhus control. Later, some of the officers in the combat units will be listed. At this point, it seems appropriate to record the names of several men who carried forward the work of the U.S.A. Typhus Commission in the European theater. These were Col. Joseph F. Sadusk, Jr., MC, Executive Officer, 26 July to 8 November 1944; Lt. Col. David M. Greeley, MC, Executive Officer, 8 November 1944 to 26 April 1946; and the special consultants, Major Woodward, Major Snyder, and Capt. (later Maj.) William A. Davis, MC, who was Typhus Liaison Officer with the British 21 Army Group. These officers had the shock and burden of dealing with typhus in the ghastly German concentration camps. Maj. George Zinnemann, MAC, handled supplies and transportation under incredibly difficult conditions.

### Epidemic Typhus in the European Theater, 1944–46

As there were only 10 cases of typhus fever and no deaths from the disease among U.S. Army troops in the European theater during the years 1942 to 1945, the problems were not those of loss of effectiveness and care of the sick. They were problems of the maintenance of the highest possible standards and practice of preventive medicine, to be judged by the resulting minimizing or absence of trouble rather than by the curbing of some holocaust of disease. They were matters of preventive medicine not only among the military forces but also among millions of refugees and displaced persons, German civilians in the Rhineland and Inner Reich, German prisoners of war, and civil and political prisoners in the German concentration camps. After the fall of Germany in May 1945, these activities were extended to the American and

British Zones of Occupied Germany, to parts of Austria, and to parts of Poland, notably Warsaw. Typhus was an ominous overhanging threat. It was held back by measures of preventive medicine applied through all traditional military channels and also through the new agencies of Civil Affairs and Military Government, and some new civilian agencies such as UNRRA.

### *France*

The 230 cases of epidemic typhus reported in France in 1942 occurred mainly in the prisons of Marseille. In 1943, only 4 cases occurred in the civilian population in France, and only 12 cases in this group in 1944. In addition, outbreaks of typhus are reported to have occurred in camps of foreign labor drafted by the Germans—61 cases near Metz and 250 cases among Russian (Todt) laborers in the Cherbourg area in the period from January to July, 1944.<sup>72</sup> These gave rise to disturbing rumors when the invading force learned about them in June 1944, but there were no authenticated cases of typhus in France at this time. None occurred until about a year later when at the camp for refugees and returning nationals at La Courtine, in late February 1945, several cases of typhus occurred. Maj. Lucien Brumpt of the French Army and representatives of the U.S.A. Typhus Commission instituted adequate control measures here.

### *Belgium, Luxembourg, and Holland*

No cases of typhus occurred from D-day through 1944, but as a precautionary measure, refugees returning to their homes, foreign Todt workers left behind by the retreating Germans, and political prisoners in local jails were deloused. As the advance progressed and more portions of these countries were liberated, an increasing number of refugees and displaced persons, louse-infested, returned to their homelands. They brought typhus with them. For example, from March to June 1945, 136 cases were reported in Belgium and 49 in the Netherlands. By 1945, effective procedures for handling displaced persons were in operation, and typhus did not spread in these areas.

### *The Rhineland*

The mutton-leg-shaped area, bordered on the east by the Rhine River from Switzerland to the North Sea, on the south by France, and on the west by Luxembourg, Belgium, and Holland, constituted a natural division of Germany, according to the political situation in 1944. This was called "the Rhineland." Its capture in order to aline the Allied armies along the length of the Rhine preparatory to the assault upon the heart of Germany was a major objective of the campaign. As soon as the Battle of the Bulge ended in the Allied victory in the Ardennes in January 1945, moves were made toward the assault on the Rhine. In doing so, contact was made for the first time with epidemic typhus in western Europe in an area which had been free from the disease for many years.

<sup>72</sup> Epidemiol. Inform. Bull., United Nations Relief and Rehabilitation Administration, Health Division 1 (No. 7) : 296, 319, 322, April 1945.

Summarizing Colonel Gordon's report and using much of his language with only occasional quotation marks, the following is an account of the rise and suppression of the epidemic in the Rhineland:

**Aachen.**—Typhus was first reported in the Rhineland by the 10th Medical Laboratory, which was then assigned to the First U.S. Army. Several Italian conscript laborers traveling from Holland to Aachen had fallen into the hands of the Ninth U.S. Army. Four were at that time convalescent from an illness surmised to be typhus. The serological diagnosis was made at the Laboratory. The onset of the symptoms apparently dated from 15 February 1945.

**München-Gladbach.**—On 5 March 1945, the Ninth U.S. Army discovered five cases of typhus in the city of München-Gladbach. Immediately thereafter, it was found that the labor camps in the vicinity and a considerable area of the region, as well as the city, were involved. The epidemic had started in Neuss in November 1944. Of 183 cases reported, 75 were found by American troops. Russian and Polish laborers were principally affected. Fifteen native Germans contracted the disease by caring for the patients.

**Cologne.**—At about the same time in March 1945, an epidemic of typhus was uncovered in Cologne and its vicinity by medical personnel of the First U.S. Army and the Cologne Military Government detachment. A total of 199 cases occurred in Cologne up to 1 June 1945. They were scattered throughout the city, air raid shelters, and prisons.

**Hermülheim.**—As this is such a neat example of an explosive outbreak promptly quenched, Colonel Gordon's account of it is quoted:

A group of 16 Ukrainian laborers, both men and women, left Cologne in the early days of the American occupation. They stopped for 2 days in Hermülheim, population 1,600. During the 2 nights they remained in the village, they slept in an air raid shelter which cared for the residents of two streets of the town. Hermülheim had previously been free from typhus fever. The Ukrainians went their way, but subsequently two were seen in Aachen with typical typhus fever infection.

During the 2 days immediately preceding 24 March 1945, 30 German residents of the town developed typhus fever. All had used the air raid bunker in which the Ukrainians had slept.

When Hermülheim was visited that evening, the Bürgermeister and his health officer had already instituted quarantine. The following morning the entire village was deloused by dusting, and vaccinated. In the course of the following week, the number of demonstrated cases increased to 58. No secondary case occurred after the accepted incubation period. The outbreak and the control measures employed demonstrated clearly the potentialities associated with the introduction of typhus into a susceptible civilian community, and the results to be expected from prompt inauguration of modern control methods.

**The Rhine Province, Saarland, and Palatinate.**—In this region of territory contiguous to Germany west of the Rhine, about 400 cases of typhus had occurred in the weeks immediately preceding the entry of American troops. The seeding was heavy and the potentiality of spread was imminent. The following vivid description is quoted from Colonel Gordon's report:

The whole area seethed with foreign peoples, conscript laborers moving this way and that and in all directions, hoping to reach their homes, in search of food, seeking shelter. Most of the typhus was within this group and they carried the disease with



them. They moved along the highways and in country lanes—now a dozen Roumanians pulling a cart loaded with their remaining belongings; here a little band of Frenchmen working their way toward France, there some Netherlands, or perhaps Belgians; and everywhere, the varied nationalities of the East—Ukrainians, Poles, Czechs, and Russians. They moved mostly on foot, halted, then gathered in great camps of sometimes 15,000 or more, extemporized, of primitive sanitation, crowded, and with all too little sense of order or cleanliness.

These were the people where typhus predominated, more than half a million of them in the Rhineland, wearied with war, undernourished, poorly clothed, and long inured to sanitary underprivilege and low level hygiene. Add to this shifting population the hundreds of released political prisoners, often heavily infected with typhus but happily far fewer in numbers; the German refugees, first moving ahead of our troops, and then sifting back to their homes through the American lines. Rarely, if ever, has a situation existed so conducive to the spread of typhus.

Typhus fever in a stable population is bad enough. It has demonstrated its potentialities in both war and peace. The Rhineland in those days of March 1945 could scarcely be believed by those who saw it—it is beyond the appreciation of those who did not. It was Wild West, the hordes of Genghis Kahn, the Klondike gold rush, and Napoleon's retreat from Moscow all rolled up into one. Such was the typhus problem in the Rhineland.

By incessant activities of "typhus teams" and medical and sanitary personnel of military units and Civil Affairs groups having adequate supplies and using methods whose worth had been proved at Naples (case finding, isolation of cases, contact and group delousing with DDT powder, and some vaccination), the main centers of infection at München-Gladbach and Cologne were brought under control during March. Thereafter, cases in other parts of the Rhineland were held to relatively low figures. "May ended with the disease virtually absent."

During the period from March to June 1945, a total of 693 cases were reported in the Rhineland. There were 22 fresh outbreaks of the disease involving 31 villages, towns, or cities. Although the resident native population was about 7,500,000 as compared with about 500,000 displaced persons, about two-thirds of the cases, some 400, were among the latter. Infestation with lice was much more frequent among the displaced persons group than in the native population. Living quarters of the displaced were more crowded and unsanitary.

Among 388 patients about whom sufficient information was available, 61 were known to have died of typhus, giving a case fatality rate of 15.7 percent. The case fatality rate of native Germans was 35 percent while it was 3 percent among the displaced persons who were largely of Eastern European origin.

**The Inner Reich.**—For the purpose of his analysis and report, Colonel Gordon defined the Inner Reich as that part of Germany east of the Rhine and north of Switzerland which "fell under the influence of the U.S. Army." It included not only a major part of Germany, but the westernmost part of Czechoslovakia and the greater part of Austria.

The move into this region began on 7 March 1945 when the 9th Armored Division and the First U.S. Army seized the Ludendorff railroad bridge at Remagen and established a bridgehead on the east bank of the Rhine. The

massive assault across the Rhine began on 24 March, with the British 21 Army Group (Canadian First Army and British Second Army) on the north, with next in line from north to south, the Ninth U.S. Army, the First U.S. Army, the Third U.S. Army, the Seventh U.S. Army, and finally the French 1st Army opposite Strasbourg. As noted by Colonel Gordon: "All found typhus fever; the British scarcely any, the Ninth some, the First and Third a great deal, while in the south the Seventh U.S., and the 1st French Armies again encountered relatively little." Many cases of typhus fever were found in the cities, towns, and villages along the east bank of the Rhine, as in Düsseldorf, Mülheim, and Duisburg. There were also many rumors of cases which set in motion additional preventive medicine activities.

Soon after the crossing of the river, a westward reflux of displaced persons, refugees, prisoners, and others began. This movement called for special arrangements for control at the crossings.

The first large-scale measure of control was the establishment of a cordon sanitaire (or "sanitary border") extending from the political boundary of Switzerland and the Rhine River along the course of that river to the junction of the Rhine and Waal Rivers and thence along the Waal to the North Sea. All existing and future crossings were designated as either ports of entry or guard stations, and all civilians and liberated prisoners of war traveling from east to west would be deloused at these ports of entry before entering the cordon sanitaire. These arrangements were ordered by Headquarters, SHAEF, on 31 March 1945, and were implemented by a directive issued by Headquarters, ETOUSA, on 12 April. Before this, however, the armies had established delousing stations at the crossings in their respective sectors. Colonel Gordon has pointed out that the original plans for such a cordon sanitaire were drawn up in his Preventive Medicine Division, ETOUSA, in 1943. On 27 March, General Fox formally recommended a similar establishment. There were many claimants for the distinction of having initiated this protective action. As a matter of fact, the action was obvious and the idea was an old one, frequently refurbished. It had been quite clearly presented, for example, in the report of the Committee of Experts in 1937 (p. 184). Continuing to quote from Colonel Gordon's article:

Delousing stations at ports of entry were located near bridges, usually in a displaced persons center. Military police permitted civilians and liberated prisoners of war to cross only if their identification papers had the necessary endorsement showing recent disinfection. Delousing stations were maintained at entraining points for civilians moving across the Rhine, by rail, and similar provision existed for air travel.

The typhus epidemic in the Inner Reich was no orderly developing process, but a sharp increase to epidemic proportions and a progressive but more slowly ordered decline. The cases reported in a given week represented not so much the progression of the disease as the progression of the armies. The more territory that was uncovered, the greater was the number of reported cases \* \* \*. Reporting of typhus fever during the advance through Inner Germany proper was even more disorganized and irregular than it had been in the Rhineland \* \* \*. Not until late May and early June, not until the last great concentration camp came under American control, did weekly reports of typhus give indication of



the true course of the epidemic—and that course was one of satisfactory and progressive improvement.

The epidemic of typhus in the Inner Reich, or American occupied territory of Germany, lasted about 3 months, from the last week of March to the end of June 1945. During this period, a total of about 15,800 cases was reported from 518 localities in the environment of troops. Of these cases, approximately 8,800 occurred in 292 new localities and approximately 7,000 in 226 old localities. The epidemic was definitely over by the end of June. It is remarkable evidence of the residual effect of strongly applied military preventive medicine, or of some mysterious biological process, that the disease had remained suppressed in this region. There were only 32 cases reported in August 1945. "Subsequent events showed that typhus in Germany had been brought under complete control, for during the winter of 1945-46, no more than a reasonable endemic incidence prevailed."

**The German concentration camps in the Inner Reich.**—This is not the place to recapitulate descriptions which others have published about the horrors of the German concentration camps for political and Jewish prisoners. Perhaps figure 13 will be sufficient to indicate the conditions in which typhus was rife, as observed by Major Davis.

The purpose of this brief section is to record that typhus was epidemic in these camps and spread from them to the surrounding areas when the surviving inmates were able to escape. They carried typhus and lice with them. The strenuous application of modern methods of typhus control, chiefly delousing with DDT powder and some vaccination, checked the disease in about 2 weeks. In addition, clinical care by members of the U.S.A. Typhus Commission helped to save some lives by applying knowledge gained at Cairo, by relieving water starvation, and by providing adequate protein content in the diet. Chemotherapeutic studies, particularly those in which PABA was used, produced little of benefit.<sup>73</sup>

The chief concentration camps uncovered by the American and British Armies during April and early May 1945 were Belsen, Buchenwald, Dachau, Flossenbürg, and Mauthausen. There were others in addition. "All had hundreds of cases of typhus fever and sometimes thousands." Notes on two of these concentration camps, Belsen and Dachau, will be presented to illustrate problems of typhus control in such situations.

**Belsen.**—To quote from the report by Major Davis,<sup>74</sup> who was the U.S.A. Typhus Commission liaison officer with the British 21 Army Group:

The concentration camp at Belsen (in the Province of Hanover) Germany, was taken by the British Second Army on 15 April 1945. Its inhabitants, of whom about 61,000 were still living, were suffering from starvation, typhus, dysentery, tuberculosis, and other dis-

<sup>73</sup>(1) Report, A. Yeomans, D. H. Clement, C. J. D. Zarafonetis, R. A. Phillips, and J. C. Snyder, to the Director of the United States of America Typhus Commission, July 1945, subject: Activities of the United States of America Typhus Commission at Dachau Concentration Camp, 10 May to 10 June 1945. (2) Yeomans, A.: Progress in Rickettsial Disease Therapy, With Special Reference to Para-aminobenzoic Acid. *Lancet* 67: 60-63, February 1947.

<sup>74</sup>Davis, W. A.: Typhus at Belsen. I. Control of the Typhus Epidemic. *Am. J. Hyg.* 46: 66-83, July 1947.





FIGURE 13.—Starving, louse-infested, typhus-ridden civilian prisoners in filthy corridor in the German concentration camp at Belsen, April 1945.

eases. Typhus had been prevalent in the camp for 4 months, and there were approximately 3,500 cases at the time of liberation. Practically 100 percent of the internees were heavily infested with lice.

A general program for the care and feeding of the prisoners was set up. As part of this, a typhus control unit was created. All inmates of the camp were powdered with DDT powder within 9 days of the start of operations (fig. 14). Key personnel working in the camp were vaccinated, and the sick were hospitalized.

Typhus cases among the inmates of the camp stopped abruptly 14 days after the first delousing had been completed. Examination revealed that about 25 percent of the inhabitants of the camp still had lice after one delousing, but only about 3 percent were found to have lice after further treatment. There were at least 14 cases of typhus among British personnel working in the camp; these patients had been vaccinated and their disease was mild.

**Dachau.**—The Dachau Concentration Camp in Bavaria, a few kilometers north of Munich, was liberated by the Seventh U.S. Army on 1 May 1945. With



FIGURE 14.—German woman using a power duster to apply louse powder to the hair of a female prisoner at a German concentration camp, April 1945.

about 40,000 prisoners, it was smaller than Belsen, but no less horrible. No accurate record of the number of typhus patients and deaths from the disease could be obtained until later in May. Possibly they amounted to 4,000 cases. At the time of "liberation," many inmates of the camp scattered widely through the nearby country, particularly in the region south of Munich, carrying typhus and lice with them. "The camp was promptly quarantined. Hospitals were moved in to augment the small prison hospital. Case-finding teams initiated control work through survey of the surrounding area. \* \* \* The dusting of prisoners with DDT powder was started 3 May 1945, and completed 8 May. \* \* \* Immunization of prisoners against typhus was put into force as soon as conditions permitted. The primary emphasis was on delousing. In respect to case fatality, data are available for 2,336 cases reported up to 1

June. The number of patients who died was 311, and the case fatality rate was 13.3." Reference has been made already to clinical and chemotherapeutic studies made at Dachau by members of the staff of the U.S.A. Typhus Commission. According to Colonel Gordon, this outbreak of typhus at Dachau was "most difficult to control and the most serious in its epidemiologic portent."

### *Liaison with British 21 Army Group*

In accordance with a plan developed by General Fox and approved by the Public Health Branch, G-5, SHAEF, for utilization of members of the staff of the U.S.A. Typhus Commission as "typhus consultants," Captain Davis (p. 240) was detailed first to SHAEF on 27 November 1944 and immediately thereafter ordered to the Headquarters, British 21 Army Group, as a liaison officer. This Army group was composed of the Canadian First Army and the British Second Army, and had as its sector a vast area of northwest Europe. On 28 November, Captain Davis reported to Col. W. H. Crichton, R.A.M.C., Senior Civil Affairs Officer, Public Health, Headquarters, British 21 Army Group, in Brussels. It was not until 4 August 1945, after 9 months of helpful service, that he left this association and returned to the Field Headquarters of the U.S.A. Typhus Commission at Paris.

The unusual status of the U.S.A. Typhus Commission as a miscellaneous activity of the War Department, acting under a Presidential Executive order, made possible many unusual arrangements in the field of military preventive medicine among the Allied Forces. This liaison arrangement with the British 21 Army Group is an excellent example of such a boundary-crossing international relationship through which services of great value were rendered—and by a junior officer.

Some idea of the scope of the activities of this liaison officer is given by the following list of captions from his final report:<sup>75</sup>

1. Appraisal of problems and formulation of plans of action based upon inspections and visits in the British and Canadian Army areas and contacts with Belgian and Netherlands authorities (28 November to 15 December).

2. Obtaining supplies and training personnel for typhus control (16 December 1944 to 21 February 1945), meantime continuing inspection trips.

3. Appraisal of typhus control programs of the Belgian and Netherlands Governments.

4. Typhus control work when the disease appeared in the Army area and at the Rhine crossings (22 February to 18 April).

5. Combating typhus in the German concentration camps, notably Belsen, and also in Sandbostel, Neustadt, and Denmark (19 April to 3 June 1945).

6. Final stages of bringing typhus under control (3 June to 4 August 1945).

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<sup>75</sup> Report, Maj. W. A. Davis, MC, for the Director, United States of America Typhus Commission, 1 Oct. 1945, subject: United States of America Typhus Commission Liaison With the British 21 Army Group, 28 Nov. 1944 to 4 Aug. 1945.



### 7. Formulation of programs for the future in the British Enclave.

The report of Major Davis, dated 1 October 1945, concludes in part as follows:

The aim of this program, as stated earlier, has been to completely eliminate typhus from the British area. To keep all responsible parties aware of this and know the principles of the program already in effect, a memorandum for distribution from Brigadier Kennedy's office was prepared on 26 July (1945). There is every reason to believe that, with supplies adequate, personnel now trained, typhus nearly extinct in the area, and the defeat of the Nazi regime which had created concentration camps, complete victory over typhus lies within our grasp.

As a concluding summary of this portion of the experience, again statements by Colonel Gordon are quoted:

Under any interpretation of governing circumstances, much credit must be given to the efficiency of recently developed methods of typhus control, and to the cooperative effort of army agencies which assured they were executed satisfactorily. The value of delousing through dusting with DDT, and the usefulness of typhus vaccine were tried and tested on a scale greater than ever before and under conditions epidemiologically more conducive to extensive and continued spread of the disease. The results attained in the Naples epidemic were confirmed and extended.

The pre-epidemic planning was the result of integrated action by at least four agencies, the Office of the Chief Surgeon, ETO, the G-5 Public Health Section of SHAEF and its lower echelons, the Office of the Surgeon of 12th Army Group and the United States of America Typhus Commission.

No single factor contributed more to the satisfactory end of the outbreak (in the Rhineland and Inner Reich) than that never in the course of the epidemic were the fundamental supplies of DDT powder and vaccine lacking. Occasional difficulties arose in local distribution, but the supply system was such and the stockpiles so great that they were promptly remedied.

### U.S. Forces, European Theater, 1945-46

Soon after the surrender of Germany on 8 May 1945 (V-E Day), extensive reorganizations of commands and communications zones began to take place to convert the objectives of combat into the management of an occupation. These changes had relatively little effect upon the basic programs for the prevention and control of typhus fever. The well-tested principles and the lessons learned during the previous 2 years were readily carried over into the less strenuous preventive medicine practices of occupation troops and into the control measures to be applied among the civilian population in concert with the performance of units of Civil Affairs and Military Government of occupied territories. There is no need to record the actions and events in detail since by this time they were on all levels a repetition of intelligent and well-drilled arrangements and procedures.

In place of SHAEF and ETOUSA, a new command, designated USFET (U.S. Forces, European Theater) was established on 1 July 1945, with its

main headquarters at Frankfurt, Germany. General Kenner became Theater Chief Surgeon, Chief Medical Inspector of all U.S. troops and installations in USFET, and also Chief Surgeon, TSFET (Theater Service Forces, European Theater). His preventive medicine officer was Col. Tom F. Wayne, MC. At about the same time, the Office of Military Government for Germany (U.S.) placed Maj. Gen. Morrison C. Stayer, formerly Chief Surgeon, MTOUSA, in charge of its Public Health and Welfare Branch with its chief office at Frankfurt and a small forward echelon in Berlin. The U.S.A. Typhus Commission functioned in relationships with all of these organizations, but had especially close relations with General Stayer's office.

On 7 September 1945, the Commission moved its Field Headquarters from Paris to Frankfurt, settling down finally in an office building at Höchst, a few miles away. This office under Colonel Greeley as Executive Officer was maintained in this location until it was closed on 22 April 1946.

Under the supervision of Colonel Wayne and the preventive medicine officers with troops, the regular measures for the prevention of infestation with lice and immunization against typhus were rigorously enforced among the American occupying armies. There were no cases of epidemic typhus among U.S. Army personnel during this period.

Only a few cases of epidemic typhus occurred among the civilian population of occupied Germany after the middle of 1945, and louse infestation was small. Perhaps the rain of DDT louse powder that had been sprinkled over millions of persons was the reason for this result. The U.S.A. Typhus Commission was one of several agencies that maintained a constant alert on typhus and assisted in making sure that there were ample supplies of DDT, dusters, and vaccine available at all times. For instance, the Commission assisted in making the estimate that the nonmilitary requirements for DDT louse powder for the U.S. Zone in Germany for 1946 should provide 375 tons of powder—sufficient for 12 million dustings.

The Executive Officer of the Commission (Colonel Greeley) served as one of the chief advisers to the U.S. Military Government of the Berlin District with respect to typhus control. At this time, a program for typhus control among the citizens and inhabitants of Berlin was being considered. Colonel Greeley worked in consultation with American, British, French, and Russian representatives and with the Chief Health Officer of Berlin whose *Hauptgesundheitsamt* (Health Department) had stations in all *Verwaltungsbezirken* (administrative districts). The program proposed by Colonel Greeley was adopted without change and was issued in English, French, and German as a public health directive for Berlin.

Between September 1945 and April 1946, Colonel Greeley visited Stockholm, Sweden; Oslo, Norway; Copenhagen, Denmark; Prague, Czechoslovakia; and Vienna, Austria, in the cause of promoting modern methods of typhus control. A brief account of his extensive work in Poland follows.

**Poland.**—Although no U.S. Army troops were stationed in Poland during World War II or immediately thereafter, the Medical Department and related organizations of the Army were concerned with the prevention and control of epidemic typhus fever in that country from at least as early as the middle of 1944 to the closing of USFET in 1946. This concern was the natural consequence of the Army's responsibilities for civil public health affairs in liberated countries. It arose also from the necessity for taking precautions to prevent the spread of typhus from the historically epidemic region of Poland into areas of western Europe which were occupied by the U.S. Army in concert with Allied Forces. Furthermore, typhus control in Poland was required to obviate burdens that might fall upon occupying forces elsewhere as a result of the movement of millions of refugees, displaced persons, and German prisoners of war from Russia through Poland to parts of Germany occupied by the Allies.

During the war, there had been hundreds of thousands of cases of typhus in Poland. From 1944 onward, however, the incidence decreased, and there was less infestation with lice. Nevertheless, in devastated Poland, the threat of an epidemic of typhus caused considerable anxiety.

As early as October 1944, in anticipation of the liberation of Poland by Russia, a number of moves toward typhus control were started in the United States. There were inquiries as to conditions, needs, and means for dealing with the situation. While these activities were centered at headquarters of UNRRA in Washington, D.C., the Office of The Surgeon General, the Supply and Preventive Medicine Divisions of the Office of The Surgeon General, and the U.S.A. Typhus Commission became concerned with the making of plans and with provision of supplies. Large numbers of CAD antityphus units, large quantities of DDT louse powder and hundreds of dust guns (hand and power types), quantities of typhus vaccine, and miscellaneous supplies were allocated to UNRRA for use in Poland. The UNRRA Mission entered Poland in April 1945 and was constantly assisted by these Army agencies.

In Germany, General Stayer, Chief Surgeon, U.S. Group Control Council, at Frankfurt, was kept informed by the theater preventive medicine officer, Colonel Whayne, and by Colonel Greeley, Executive Officer of the Field Headquarters of the U.S.A. Typhus Commission, the office of which had been opened at Frankfurt on 27 November 1945. At the request of General Stayer, Colonel Greeley was sent on several extensive trips through Poland and Czechoslovakia. In Poland, Colonel Greeley assisted greatly in improving the distribution of DDT louse powder and typhus vaccine. He gave instructions and conducted demonstrations of individual- and mass-delousing procedures according to the latest methods, using DDT louse powder applied to persons fully clothed.

A large amount of additional political, medical, and scientific material relative to typhus in Poland is in the files of the U.S.A. Typhus Commission.



## TYPHUS IN THE NORTHEASTERN MEDITERRANEAN AREA— GREECE AND YUGOSLAVIA, 1944-45

### Greece

Although Greece in 1944 was outside the "sphere of interest" of the United States and was not included in the area of MESC until 1945, the threat of epidemic typhus on that eastern flank of the Allied Forces compelled the United States to participate to a limited extent in antityphus activities in that country. As a matter of fact, planning for such participation began in Cairo as early as March 1944 through conferences between medical officers at the British Military Headquarters (Balkans and Greece), the Office of the Chief Surgeon, USAFIME, the Field Headquarters of the U.S.A. Typhus Commission, and local representatives of UNRRA. The Office of the Chief Surgeon, MTOUSA, under General Stayer, where Colonel Stone was Preventive Medicine Officer, had final local jurisdiction over American military medical work in Greece after its liberation. The engagement of these local headquarters and units in combating typhus in an international arena involved in turn their main offices in Washington, such as the Office of The Surgeon General, the Headquarters of the U.S.A. Typhus Commission, UNRRA, FEA, the American Red Cross, and, of course, all appropriate higher departmental offices. The characteristic pattern of cooperation amidst complexities was repeated in the case of the prevention and control of typhus in Greece.

In the latter part of September 1944, Greece was liberated from the atrocious German occupation by British Forces landed in the Athens-Piraeus area under Lt. Gen. Roland Mackenzie Scobie, Commander of Allied Operations in Greece. Almost immediately, the civil war between the Rightists (Royalists) and the National Liberation Front (Communists), known as EAM, with its guerrilla ELAS, became intensified. This greatly increased the difficulties and dangers of all operations, including the making of epidemiological surveys and the initiation of a typhus control program.

With the approval of General Stayer, Capt. (later Maj.) Chris J. D. Zarafonetis, MC, of the staff of the Field Headquarters of the U.S.A. Typhus Commission at Cairo was attached on temporary duty status to Military Headquarters (Greece). He arrived in Athens on 10 December 1944. Because of the street fighting in the city and raids in the country, it was not possible to carry out surveys for typhus at the start. There were many difficulties in securing and distributing supplies. For example, a shipment of Hudson dusters turned out to be composed of the toy models known as "cockroach chasers." Shipments of DDT and typhus vaccine went to the wrong ports or were lost in transit. By strenuous work, however, Captain Zarafonetis, as the chief adviser on matters of typhus control, was able to organize committees to work in collaboration with the revived Ministry of Hygiene to formulate<sup>76</sup> and commence

<sup>76</sup> Memorandum, Capt. C. J. D. Zarafonetis, MC, Public Health Department, Headquarters, ML (Greece), C.M.F., to Brig. Gen. Leon A. Fox, Field Director, United States of America Typhus Commission, Medical Section, Headquarters, U.S. Army Forces in the Middle East, 18 Dec. 1944, subject: Typhus Situation in Greece.

a program for typhus control among civilians in spite of the obstacles of dirt and degradation. By the time of his departure on 23 February 1945, improvements were progressing, safeguards had been strengthened, and sufficient anti-typhus supplies were passing into Greece.

While in Greece, Captain Zarafonitis established an important scientific relationship with Dr. J. Caminopetros, Director of the Institut Pasteur Hellenique in Athens. Valuable information and sera and rickettsial strains from both epidemic and murine typhus were obtained from the Institute and sent to Washington for study. Dr. Caminopetros supplied also a specimen of blood containing his "virus of Balkan grippé." The micro-organism in this specimen was identified by the Commission on Acute Respiratory Diseases, Army Epidemiological Board, as the rickettsial agent of Q fever (*Rickettsia burneti*).<sup>77</sup> Since its isolation, this strain has been used for important experimental work in the Army.

### Yugoslavia

The history of typhus during World War II in Serbia, Croatia, and the combined countries finally called Yugoslavia, deserves a separate volume. It cannot be presented adequately without accounts of the fight against the Nazis, the civil war within the region, the distressing social, economic, and sanitary conditions, the sturdy moral fiber of the brave people, the influence of leaders (notably Josip Broz who became Marshal Tito and Head of the Government), the strategic plans of the Allies, and the pull and haul of conflicting international interests which to some degree became Balkanized by contact with the traditionally inharmonious relationships in the area. It is to be recalled that a route for invading Allied Forces through this region was regarded for awhile as the way to "the soft underbelly of the Axis," preferable to some to the route through Italy. All these matters of high policy, as well as innumerable details of the operations of medical and military units, influenced the planning and actions taken for the prevention and control of typhus in Yugoslavia.

Obviously, there is no room for such an account in this volume. Furthermore, some feel that as there were no U.S. Army troops in Yugoslavia, there is little reason to devote much space to the subject. The author accepts that point of view and will reduce the mass of records to a minimal mention.<sup>78</sup>

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<sup>77</sup> Commission on Acute Respiratory Diseases, Army Epidemiological Board. Identification and Characteristics of the Balkan Grippé Strain of *Rickettsia burneti*. Am. J. Hyg. 44: 110-122, July 1946.

<sup>78</sup> Full documentation and many reports about typhus in Yugoslavia during World War II are in the files of the U.S.A. Typhus Commission, The Historical Unit, Army Medical Service. Special reference is made to the following folders and reports: (1) See U.S.A. Typhus Commission files—Balkans I—12 Mar.—6 Sept. 1944; Balkans II—8 Aug. 1944—24 May 1945. (2) See U.S.A. Typhus Commission files—Yugoslavia—Series of Twelve Reports by Lt. Col. E. S. Murray, MC, to Brig. Gen. Leon A. Fox, Field Director, U.S.A. Typhus Commission, for the period January 1945 to 15 July 1945. (3) See U.S.A. Typhus Commission files, Field Headquarters, Typhus Commission, Headquarters, U.S. Army Forces in the Middle East, Cairo, Egypt, 1943-45. (4) Manuscript volume (137 pp.) entitled "Yugoslavia," by Capt. A. J. Waring, MC, member of the staff of the Headquarters, U.S.A. Typhus Commission, Washington, D.C., historical report written during the first quarter of 1946.

As the most devastating epidemic of typhus in modern times had started in Serbia in 1915, and as typhus continued to occur in the Balkans, the region of Yugoslavia was of special interest to the U.S.A. Typhus Commission. The Commission, as well as The Surgeon General and many other Army medical officers, was well aware of the danger that typhus might spread from the Balkans to other Mediterranean areas. In fact, this did occur. Although there were no Allied troops in Yugoslavia, typhus coming from that country jeopardized the military operations of the Fifth U.S. Army and other Allied Forces in southern Italy in 1943-44. One source of the outbreak of typhus in Naples in October 1943 was the group of Serbian prisoners of war who had been confined in the Poggioreale Prison near that city. The continued influx of refugees from the Balkans into Italy maintained the threat of typhus.

Starting in 1943, attempts were made by the U.S.A. Typhus Commission to obtain permission from the War Department to place a typhus control team in Yugoslavia. These attempts were blocked repeatedly at the level of the General Staff for reasons that were not clear at the time to the medically motivated members of the Commission. Later, it became apparent that Yugoslavia was primarily in the British-Russian sphere of interest and that the United States should stay out. This is illustrated by the following notation by Sir Winston S. Churchill<sup>79</sup> in his record of the Moscow Conference of 9-11 October 1944:

The moment was apt for business, so I said [to Stalin]: "Let us settle about our affairs in the Balkans. Your armies are in Rumania and Bulgaria. We have interests, missions, and agents there. Don't let us get at cross-purposes in small ways. So far as Britain and Russia are concerned, how would it do for you to have 90 percent predominance in Rumania, and for us to have 90 percent say in Greece, and go 50-50 about Yugoslavia?"

Stalin agreed. This "50-50" arrangement between Britain and Russia, leaving out the United States, explains why it took so long to get clearance for General Fox and members of the staff of the Commission to go into Yugoslavia to help the people there to initiate modern methods of typhus control.

Final authorization for participation of the Commission in typhus control in the Balkans was contained in Radiogram No. WARX 81526, 14 August 1944, from the Combined Chiefs of Staff, Combined Civil Affairs Committee, Operations Division. This authorization by no means solved all of the problems and difficulties, most of which arose from a misconception of the meaning of the attachment of the Commission to the British Military Headquarters (Balkans) and from jurisdictional conflicts between the medical establishment at AFHQ and Headquarters, MTOUSA, at Caserta, Italy, and the U.S.A. Typhus Commission in its capacity as an activity of the War Department. In the end, these were settled amicably enough.

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<sup>79</sup> Churchill, Winston S.: *Triumph and Tragedy*. Boston: Houghton Mifflin Company, 1953, p. 227.



After negotiations with a number of representatives of the Yugoslav Government in London, General Fox, Field Director of the U.S.A. Typhus Commission, met Marshal Tito at Belgrade on 13 January 1945. These two men understood each other at once, and the Marshal gave an approval that was never changed for work by the Commission on typhus control in Yugoslavia.

The work was carried forward vigorously with DDT, dust guns, and vaccine flown in by General Fox. The people were eager to learn the new methods, were readily trained, and soon organized their own typhus control units. Beneficial sanitary and scientific results were obtained, and collaborative research with American investigators has continued for the past 12 years. The Commission's team was withdrawn from Yugoslavia about 16 June 1945.

It is regretted that space is not available for tributes to the individuals who accomplished so much under difficult conditions. It is fitting, however, to record here that one of the group, Lt. Stafford M. Wheeler, MC, USNR, was killed when a landmine exploded under the U.S.A. Typhus Commission jeep on the road near the village of Zenica, northwest of Sarajevo, on 13 April 1945.

### Rumania

In December 1944,<sup>80</sup> reports were received through the State Department that 30,000 cases of epidemic typhus had occurred in Moldavia and in various places in Rumania. This presented a new threat to the Allied military operations, particularly to Russian Forces then moving through Rumania into Hungary. The situation was of concern to the U.S. Military Mission at Bucharest, to General Stayer, Chief Surgeon of MTOUSA at Caserta, Italy, and to the Field Headquarters of the U.S.A. Typhus Commission at Cairo. The services of the Commission under General Fox were requested for assistance in organizing typhus control in Rumania in collaboration with the Russians. The Commission provided instructions and helped to make antityphus supplies available, but no member of its staff entered Rumania. Finally, the chief assistance was rendered by UNRRA from January to June 1945.

### Russia

Several folders in the files of the U.S.A. Typhus Commission contain the evidence of the considerable exchange of information about epidemic typhus fever that passed between various British, American, and Russian organizations and individuals. This was somewhat one sided as far as the United States was concerned, and little new information was furnished by the Russians about the prevalence of typhus or about its control in the Soviet Union. The general tenor of their reports was that typhus did not present a serious problem. However, the Russians were glad to receive small samples of DDT at first followed by large amounts later, and they accepted supplies of Cox-type typhus

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<sup>80</sup> For reports and correspondence regarding typhus in Rumania, see the files of the United States of America Typhus Commission on deposit in The Historical Unit, Army Medical Service.

vaccine. In return, they supplied sera and some strains of *Rickettsiae*. The Russians declined to permit representatives of the U.S.A. Typhus Commission to visit Russia. On the other hand, the Commission in collaboration with the International Health Division of the Rockefeller Foundation brought to this country for a visit lasting 4 months the distinguished Russian virologists Dr. Anatol A. Smorodintsev and Dr. Valentine I. Soloviev. They came from Moscow by way of Cairo and were in the United States from March to June 1944.

### EPIDEMIC TYPHUS IN U.S. ARMY FORCES, PACIFIC—JAPAN AND KOREA, 1945-46

In all major respects, the experience of the Army with epidemic louse-borne typhus in the Far East was similar to its contest with the disease in North Africa, Italy, and Europe. By the application of the well-known principles and procedures which had been proved to be effective in NATOUSA and ETOUSA, excellent prevention and control of typhus among military personnel were achieved in USAFPAC (U.S. Army Forces, Pacific). The general occurrence of the disease among the civilian populations of Japan and Korea, and its rise to a severe epidemic in Japan, created environmental dangers for the troops stationed in the midst of the almost incredible migrations, distress, and disorganization of the Japanese people.

As in the other theaters of operations, there were only a few mild cases of typhus among the troops while there were thousands of cases among the native civilians. Hence, the control activities were directed primarily against civil conditions. In carrying out this work, however, the military and their associated medical units bore the burden of the task. The main types of the participating organizations were the same as those engaged on the other side of the world. The chief differences were in the composition and organization of the U.S. Army Forces, the characters of some of the commanding personalities, and the fact that the war was over when combat of the disease had to be undertaken by a military force whose objective was the demilitarization and occupation of the country of a defeated enemy.

An individuality of these antityphus activities developed naturally from the peculiarities of their Asiatic setting. It is regretted that the voluminous records must be reduced to such a bare summary in this chapter that their flavor will be largely lost.

The U.S. Army Forces, Pacific, made its first contact with epidemic louseborne typhus in Japan and Korea as soon as the occupation began on 5 September 1945. The Eighth U.S. Army, occupying the northern half of the island of Honshu, moved into an area which had been infected by Korean slave laborers who had escaped from the coal mines on Hokkaido in August and carried their lice and typhus *Rickettsia* with them. The Sixth U.S. Army, occupying the southern half of Honshu, was less exposed to the disease during

the last months of 1945 before it was inactivated at the end of the year. The XXIV Corps made contact with typhus in Korea when its advance party landed at Jinsen on 8 September 1945.

These forces were not unprepared to cope with epidemic typhus although they had not been exposed to it during their previous campaigns from New Guinea through the Philippines, from 1943 to the middle of 1945, nor were U.S. Army personnel exposed to typhus during the Okinawa campaign from 1 April to 22 June 1945. The soldiers had been immunized with improved typhus vaccine, were well supplied with DDT louse powder, were instructed in personal hygiene and warned against risks, and were free from lice.

## Japan

Planning for the invasion of Japan (Operation OLYMPIC), intensified in July 1945, included provision for defense against epidemic typhus. Medical and military headquarters and all appropriate units in Washington and Manila gave careful consideration to methods, means, supplies, and policies for the prevention and control of typhus, not only among invading troops but also among the Japanese and Korean people. Even before June 1945, thought had been given in the G-1 (Personnel) Section of USAFPOA (U.S. Army Forces, Pacific Ocean Areas) to the possible needs of Civil Affairs and Military Government for antityphus supplies for use in Japan and Korea, in preparation for the time when civil affairs planning would be taken up by USAFPAC in Manila.

To present the full account, the period to be covered by this section must be extended to 1 July 1946. The main sources to be utilized are listed in the footnote.<sup>81</sup>

During the period from 1 June 1945 to 1 July 1946, the principal U.S. military and Japanese civilian organizations that were concerned with typhus control in USAFPAC, with special reference to Japan, together with brief indications of their activities, were as follows:

### 1. U.S. Army:

a. *Eighth U.S. Army*.—In July 1945, the Army Surgeon, Brig. Gen. George W. Rice, recognized that typhus would constitute a definite hazard, not only to troops but particularly to civilians. He made plans for using his

<sup>81</sup>(1) Annual Report, Surgeon, Eighth U.S. Army, 1946. (2) Public Health and Welfare in Japan. General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section. [A historical background and presurrender status of health and welfare in Japan, in addition to a factual review of the progress made from the beginning of the occupation through 31 Dec. 1948. Included therein as an Annex (in two parts) is a Provisional Summary of Health Statistics for 1948 (annex and charts) and a Summary of Historical Health Data (tables) for Japan covering the period 1900-1948, prepared under the direction of Col. Crawford F. Sams, MC, Chief, Public Health and Welfare Section (SCAP).] (3) Scoville, A. B.: Epidemic Typhus Fever in Japan and Korea. In *Rickettsial Diseases of Man*. Washington: American Association for the Advancement of Science, 1948, pp. 28-35. (4) Files of the United States of America Typhus Commission on deposit in The Historical Unit, Army Medical Service, including: Report of U.S. Army Forces in the Pacific, Field Headquarters, U.S.A. Typhus Commission, by Maj. T. O. Berge, SnC, Maj. F. S. Blanton, SnC, Maj. F. W. Chorpennig, MAC, 1st Lt. M. C. Gephardt, MC, Maj. A. B. Scoville, MC, and Lt. Col. C. M. Wheeler, SnC, 26 May 1946.



malaria control units for typhus control, to supply medical officers for this purpose, to train personnel, and to acquire supplies of typhus vaccine and DDT louse powder. These plans were effectively carried out in Japan in accordance with that part of the medical mission of the Eighth U.S. Army which was to provide and supervise a preventive medicine program for the occupation forces.

b. *General Headquarters, U.S. Army Forces, Pacific.*—In June 1945, the Chief Surgeon, Brig. Gen. Guy B. Denit, and his chief preventive medicine officer, Col. Maurice G. Pincoffs, MC, at their office in Manila, had to deal with vast problems of public health in the Philippines while preparing for the medical support of the invasion of Japan. Throughout the next 12 months, close liaison was maintained with Preventive Medicine Service, Office of The Surgeon General, and with Headquarters, U.S.A. Typhus Commission at Washington. Shortly after the surrender of Japan, the Office of the Chief Surgeon moved from Manila to Tokyo with General Headquarters, USAFPAC (Advanced), in the latter part of August 1945. This office became an important coordinating center for typhus control in the Far East.

c. *The U.S.A. Typhus Commission.*—With the approval of the War Department and the theater of operations, in June 1945, a Field Headquarters of the U.S.A. Typhus Commission was established in USAFPAC. Col. Joseph F. Sadusk, MC, as Executive Officer, arrived in Manila on 28 June 1945, organized the office as an attachment to the Office of the Chief Surgeon, General Headquarters, USAFPAC, and later moved this Field Headquarters to Tokyo, still attached to General Headquarters, USAFPAC, Advanced Echelon of the Office of the Chief Surgeon. The Commission's office was opened in the Dai Ichi Building in Tokyo, Japan, on 3 October 1945, where it remained until it was closed on 15 May 1946.

The status of the Commission as a War Department activity authorized by the Presidential Executive Order No. 9285 had been established in the usual way by notification radioed to the commanding general of the theater (USAFAC), with request for logistical support.<sup>82</sup> The Field Headquarters of the Commission in USAFPAC functioned much as did the Field Headquarters in other theaters of operations, except that the personnel was more than customarily engaged in direct activities of typhus control.

In addition to participating in and supervising typhus control activities throughout Japan, the members of the Commission's staff helped to establish policy, drafted circular letters about typhus,<sup>83</sup> trained American and Japanese personnel in modern methods of delousing and typhus control, gave lectures to Japanese groups, prepared estimates of needs for supplies, facilitated shipments of supplies, and conducted scientific investigations. The Commission

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<sup>82</sup> Radiogram No. WAR 53023, signed WARCOS, Operations Division, War Department General Staff, to Commander in Chief, Army Forces Pacific Command, Manila, P.I., dated 21 Aug. 1945.

<sup>83</sup> (1) Circular No. 32, General Headquarters, U.S. Army Forces, Pacific, 2 Aug. 1945, subject: Immunization. (2) Circular No. 78, General Headquarters, U.S. Army Forces, Pacific, 26 Sept. 1945, subject: Immunization. (3) Circular Letter No. 49, Office of the Chief Surgeon, General Headquarters, U.S. Army Forces, Pacific, 12 Nov. 1945, subject: Louse-Borne Typhus.

collaborated to the limit with all agencies concerned with the prevention and control of typhus fever.

d. *Public Health and Welfare Section, General Headquarters, SCAP (Supreme Commander for the Allied Powers).*—In General Headquarters, USAFPAC, General Order No. 224, dated 4 October 1945, the discontinuance of the Military Government Section was announced. In General Headquarters, SCAP, General Order No. 1, dated 2 October 1945, the establishment of a "General Headquarters of the Supreme Commander for the Allied Powers" was announced by General MacArthur. There followed a series of General Orders of which No. 7 established the Public Health and Welfare Section, SCAP. Colonel Sams was assigned chief of this Section and became the chief health officer of Japan. While the Field Headquarters of the U.S.A. Typhus Commission remained attached to the Office of the Chief Surgeon, General Headquarters, USAFPAC, it had constant, cordial, and fruitful collaborative relationships with the Public Health and Welfare Section of SCAP.

## 2. Japanese organizations:

a. *Ministry of Health and Welfare.*—"Prior to the termination of the war," according to Colonel Sams,<sup>84</sup> "such health and welfare activities as existed in Japan were primitive in nature and ineffective in practice. A Ministry of Health and Welfare was established in 1938 \* \* \*. Within the prefectural or state organizations, health sections were in most instances under police control. On the local level, such health and sanitation activities as existed were carried out by the police and the neighborhood associations \* \* \*. Health Centers had been established in 1930, but these were primarily advisory clinics for tuberculosis and child hygiene. These Centers had neither the organization, staff, nor authority to carry out public health functions as considered necessary in a modern public health program."

b. *Government Institute of Infectious Diseases.*—Good relations were established between the U.S.A. Typhus Commission and this Japanese scientific institute. Through this connection, both before and after the 406th Medical General Laboratory was set up, serological surveys were conducted, strains of *Rickettsiae* were identified, and the production of typhus vaccine in Japan was encouraged.

c. *Industrial plants.*—Collaboration with the Nippon Soda Co., and similar firms, led to the independent production of DDT and manufacture of DDT louse powder in Japan in 1946.

From this point on, conditions and antityphus activities will be described without a close appraisal of the work and contributions of the various organizations and individuals just mentioned. It was a genuinely collaborative undertaking and will be treated as such.

## *The epidemic of 1945-46*

Although the risk of typhus in Japan had not been minimized during the planning period, its extent had been misjudged and its effect was com-

<sup>84</sup> See footnote 81(2), p. 257.

pounded by some mistakes. The extreme disorganization of civil affairs in Japan, the hordes of displaced, repatriated, and wandering people moving about the country and pouring in from Korea, and the lack of supplies occasioned by theater policy, conflicting orders, and vagaries of shipments had not been anticipated. Typhus got out of hand and the most severe epidemic of the disease in a half century among the Japanese people occurred in the winter of 1945 and spring of 1946. Although this outbreak had not been anticipated, it was suppressed so promptly that the achievement constituted another triumph of modern military preventive medicine ranking with the exploit of Naples.

Before the American occupation, the reporting of cases of typhus in Japan was unsatisfactory because both epidemic and murine, and sometimes tsutsugamushi disease (scrub typhus), were included under the single name of "typhus." The statistics are to be considered as approximate indicators of trends, although the 31,000 and more cases in 1946 are to be regarded as predominantly epidemic louseborne typhus. The statistics, for what they are worth, for the years 1941-48 are presented in table 37, and shown graphically for the years 1941-46 in chart 13.

TABLE 37.—*Reported cases of typhus fever group in Japan, 1941-48*

Year	Reported cases	Approximate rates per 100,000 population	Deaths	Approximate case fatality ratio (percent)
1941-----	42	( <sup>1</sup> )	21	50
1942-----	20	( <sup>1</sup> )	33	-----
1943-----	1, 319	2	160	12
1944-----	3, 879	5	600	15
1945-----	2, 426	3	246	14
1946-----	31, 110	41	2, 899	9
1947-----	1, 064	1	195	18
1948-----	429	1	25	6

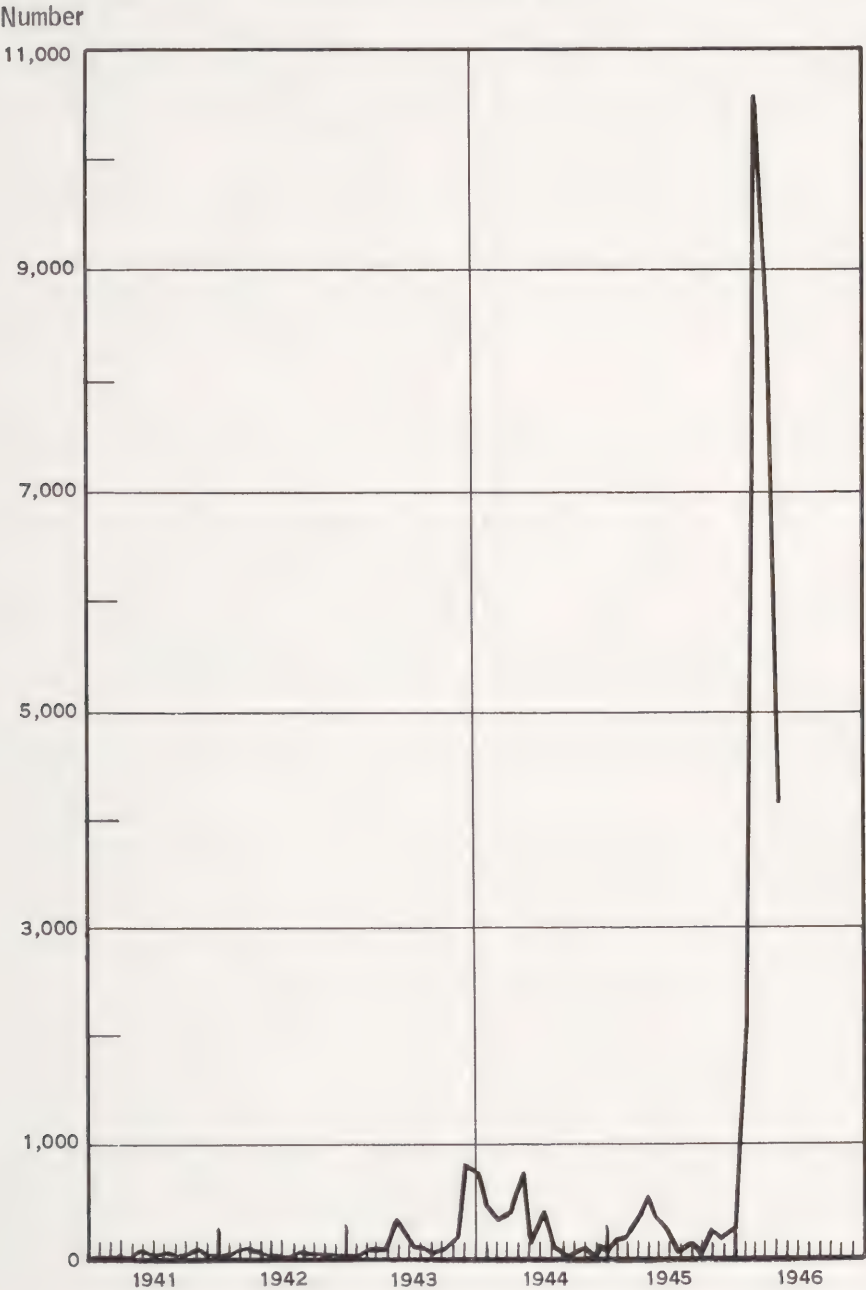
<sup>1</sup> Less than 0.5.

Source: Public Health and Welfare in Japan. A report by Col. Crawford F. Sams, MC, Chief, Public Health and Welfare Section, General Headquarters, SCAP (Supreme Commander for the Allied Powers), Tokyo, 31 Dec. 1948. (Modified by subtraction of cases and deaths from tsutsugamushi disease (scrub typhus) and by recalculation of rates.)

The predisposing conditions were those of the traditional background of a typhus epidemic. There was a serious shortage of housing due to the cessation of building during the war and the destruction of dwellings by bombing. Many persons were homeless. One-family homes became many-family shelters. The housing shortage and the shortages of food were aggravated by the postwar influx of thousands of repatriates returning to Japan from Korea, Manchuria, China, and the Philippines. Thousands who had moved to the countryside to avoid bombings were returning to the overcrowded cities. The transportation systems were overtaxed. Trains, subways, streetcars, and buses



CHART 13.—Occurrence of typhus in Japan from January 1941 to May 1946, showing the abrupt rise and fall of the severe epidemic with approximately 30,000 reported cases from December 1945 to May 1946



were so crowded that lice and louse feces could be transferred easily from person to person. Personal cleanliness was well-nigh impossible because of lack of soap and bathing facilities. Lousiness increased. There were millions of migrants, including typhus-infested people from Hokkaido and other places, coming into the repatriation ports. The Japanese public health departments were incapable of coping with the situation. Physicians and civilians generally were apathetic regarding public health and epidemic control. Anti-typhus supplies were inadequate.

During the first week in November 1945, 150 cases of typhus fever were reported from the island of Hokkaido and a few sporadic cases in northern Honshu probably attributable to infected Korean coal miners who had escaped from the mines at Yūbari during August 1945. Extensive delousing with DDT and the administration of typhus vaccine brought this outbreak under control quickly, and spread of the disease was prevented by quarantine of Yūbari.

During December 1945, outbreaks of epidemic typhus began to occur in three widely separated areas of Japan; namely, Yamagata, Osaka, and Tokyo.

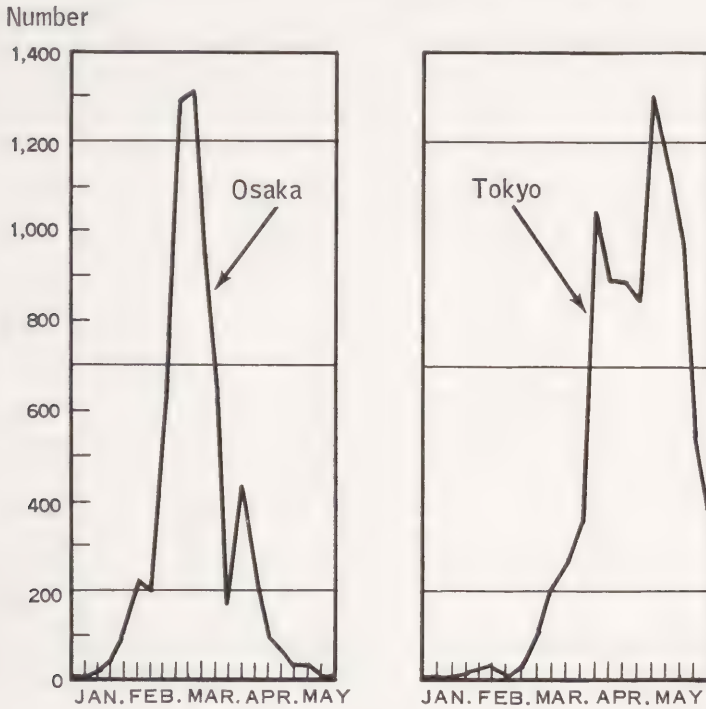
In Yamagata Prefecture in north-central Honshu, typhus fever occurred in some of its mountain villages among Japanese recently repatriated from Korea. Delousing and other control measures, including quarantine, cut the outbreak short and prevented the spread of the disease to other areas of Japan.

The outbreak in Osaka originated in one of the city jails in mid-January 1946. The case was not reported for 2½ weeks. Following the release of this man and his fellow prisoners, widespread dissemination of lice and infection took place. Ineffective focal delousing was used at first, but as the number of cases increased, mass delousing was added to contact and zonal delousing. The outbreak reached a peak of 1,300 cases reported in the first week in March 1946. Thereafter, it decreased rapidly. Before control was established, however, typhus spread from Osaka to other portions of Japan, especially to the neighboring cities of Kōbe, Kyōto, and Nagoya. The disease spread also from Osaka to Tokyo and then to Nagasaki in southern Kyushu and to Aomori in northern Honshu. An outbreak of typhus fever in Yokohama undoubtedly originated in Tokyo, as did a small outbreak in Nikkō.

The graphs of the epidemics of typhus in Osaka and Tokyo in 1946 are shown in chart 14.

Antityphus supplies, which had been held up by conflicting theater orders, began to arrive in good quantities in January 1946, as the result of the intervention of the U.S.A. Typhus Commission. Teams of American military personnel and Japanese civilians were organized and trained by the staff of the U.S.A. Typhus Commission and other organizations. A modern control program was enforced vigorously in the infected cities, areas, and at 10 main ports through which more than 2 million repatriates were processed. The control measures were essentially the same as those that had been applied successfully in Naples and in the Rhineland. It is not necessary to describe

CHART 14.—*Reported cases of typhus in the outbreaks of epidemic typhus at Osaka and Tokyo, Japan, January–May 1946*



them again here. Some variations occurred naturally to suit the local situations in Japan.

The epidemic reached a peak of approximately 2,450 cases reported in the week ending 6 April 1946, when a total of 15,335 cases had been reported since the first week in January. Thereafter, with some ups and downs, the epidemic declined, and was regarded as being definitely under control by the early part of May. This was about a month earlier than might have been anticipated from the usual seasonal decline of typhus in Japan. Although the available statistics are neither complete nor reconcilable, it is reasonable to estimate that about 29,000 cases were reported during the period from November 1945 to 30 June 1946, and that the total number of cases of typhus reported among Japanese civilians for the year 1946 was 31,110, as stated by Colonel Sams.

Clinical, epidemiological, and laboratory studies, including isolation of *R. prowazeki* from the blood of patients, and positive results of specific rickettsial complement fixation reaction proved that the epidemic of 1945–46 was classical louseborne typhus fever.

#### *Typhus in military personnel in Japan*

The protection of U.S. Army personnel against typhus was highly effective in the midst of considerable exposure. The men were well immunized, louse



free, provided with DDT louse powder, warned against risks, and kept away from known foci of infection. During the first 6 months of 1946, when the disease was epidemic among civilians, only 12 cases of louseborne typhus were reported in military personnel of the occupation forces. Two more cases (one of which was that of an officer of the U.S.A. Typhus Commission who contracted the disease from infected dust at Yūbari) had their illnesses in the continental United States, having been flown from Japan into this country while they were in the incubation period of the infection. These 14 cases are not listed in table 33 because they occurred after the close of the statistical period, 1942-45. Most of these cases were mild, as was to have been expected in vaccinated men. There were no deaths from typhus fever in this group.

### Korea

When the advance party of the XXIV Corps landed at Jinsen, Korea, on 8 September 1945, it was known that the troops would be exposed to epidemic typhus. At that time, however, the degree of prevalence of the disease in either the whole of the country or southern Korea below the 38° parallel of latitude was not accurately known. While all the usual precautions and protective measures were taken from the start of the occupation, surveys were quickly gotten underway. These surveys and future control programs based upon them were carried out thoroughly by constant collaboration between the Office of the Surgeon, XXIV Corps, the Public Health and Welfare Section, General Headquarters, SCAP, and the U.S.A. Typhus Commission. Full information on this subject can be found in the documents listed in the footnote.<sup>85</sup>

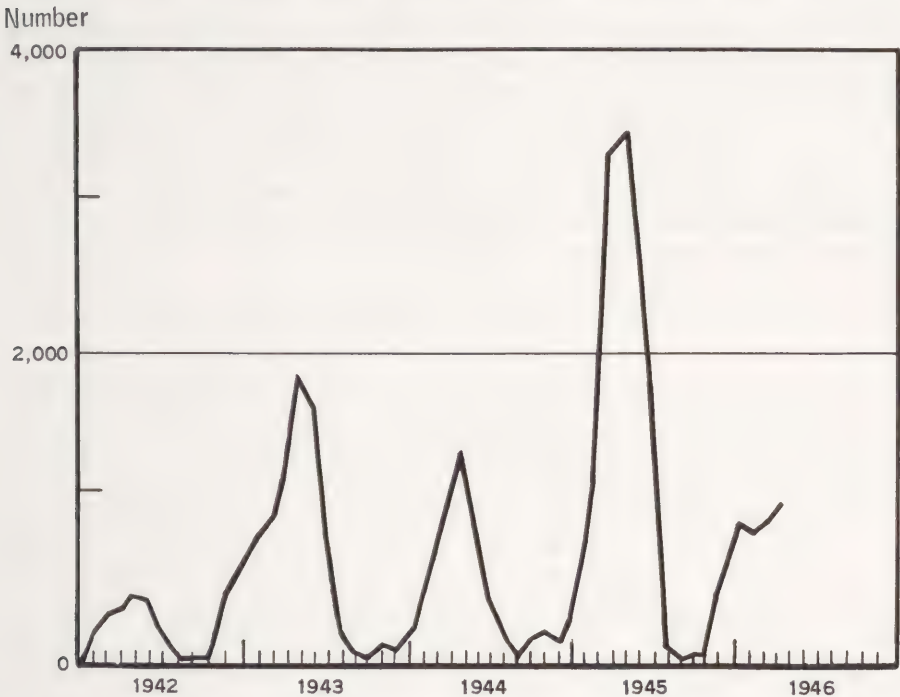
The incidence of reported cases of typhus—epidemic included with about 20 percent murine typhus—in southern Korea by years from 1942 to 30 April 1946 was as follows: 1942, 2,385 cases; 1943, 8,050 cases; 1944, 5,145 cases; 1945, 14,130 cases; and 1946 through 30 April, 3,674 cases. The approximate seasonal distribution of these cases is shown in chart 15. There was an annual rise starting in November reaching a peak in May, and declining to almost zero in July.

The situations were manageable and were well handled in accordance with the established principles and procedures for typhus control that have been described at length in antecedent sections of this chapter. They were varied,

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<sup>85</sup> (1) See footnote 81 (1-4), p. 257. (2) Memorandum, Col. Joseph F. Sadusk, Jr., Executive Officer, U.S.A. Typhus Commission, Field Headquarters, Tokyo, for Chief Surgeon, General Headquarters, U.S. Army Forces, Pacific, 27 Oct. 1945, subject: Report on Typhus Survey in Korea. (3) Memorandum, Lt. Col. Charles M. Wheeler, SnC, Executive Officer, U.S.A. Typhus Commission, for Chief Surgeon, General Headquarters, U.S. Army Forces, Pacific (Adv), 26 Dec. 1945, subject: Report of U.S.A. Typhus Commission Activities in Korea. (4) Essential Technical Medical Data, U.S. Army Forces, Pacific, for November 1945, dated 15 Jan. 1946. (5) Reports from Office of the Surgeon (Col. William D. Willis, MC), Headquarters, XXIV Corps: (1) Quarterly Report, Surgeon, XXIV Corps, USAFWESPAC, 1 Oct. 1945-31 Dec. 1945. (2) Report, Col. W. D. Willis, MC, Surgeon, XXIV Corps, to Chief Surgeon, U.S. Army Forces, Pacific, 7 Oct. 1946, subject: History of Medical Activities of ASCOM from 1 Jan. 1946 to 1 Apr. 1946. (3) Annual Report, Surgeon XXIV Corps, 1946.

CHART 15.—*Reported cases of typhus in Korea, 1942 through April 1946*



of course, to suit local conditions and the processing of millions of repatriates and refugees, but these variations need not be recounted here. The good results achieved were succinctly stated by Scoville.<sup>86</sup>

During the season 1945-46, although cases of the disease were reported from all sections of the American Zone, no large-scale outbreaks of typhus fever occurred in any Korean city. Two reasons for the failure of large epidemics to develop in this country are apparent. First, was the instruction program of typhus control instituted early in November 1945, by the XXIV Corps, Military Government, and the United States of America Typhus Commission. In this program every city which had been or was likely to be a focus of typhus was visited. In each of these cities, both Korean and American personnel were taught typhus control procedures so that potential epidemics could be forestalled. Second, in the large cities, all foci of typhus fever during previous years were demarcated and the inhabitants of these areas were vaccinated with typhus vaccine and deloused with DDT at monthly intervals. Although most of the cases of typhus fever which occurred in the American Zone were infected in northern Korea and Manchuria, a small number came from Japan. Those cases which occurred in the northern portion of the American Zone probably originated in areas which had been endemic foci for years.

During the period from September 1945 to the end of 1946, only 10 mild cases of typhus, with no deaths from the disease, occurred among U.S. Army personnel in southern Korea.

<sup>86</sup> See footnote 81(3), p. 257.

## Part II. Murine (Endemic) Fleaborne Typhus

It is the purpose of part II to deal with the second variety of exanthematic typhus fever which has been called New World or endemic typhus and is now more generally known as murine fleaborne typhus in recognition of its rodent reservoir and arthropod vector. The account will be much shorter than the history of epidemic louseborne typhus in World War II because the disease, although worldwide in occurrence and a cause of death, did not have the international significance or capacity to spread among human beings that made its congener so notorious.

### HISTORICAL AND SCIENTIFIC REVIEW

During a century or more before 1926, it had been recognized that a mild form of typhus fever was occurring in portions of the continental United States and in Central and South America, Europe, Africa, and Asia. This disease received so many designations and the confusion was so great that the true conditions cannot be extracted from the records of those past days. Clarification began in 1926 when Maxcy<sup>87</sup> concluded from epidemiological studies that "a disease clinically indistinguishable from typhus fever, except with regard to its relative mildness and low fatality rate, was endemic in the southeastern United States \* \* \* that a reservoir of infection existed other than in man, and that this reservoir was in rodents, probably rats or mice, with accidental transmission to man through the bite of some parasitic bloodsucking arthropod—fleas, mites, or possibly ticks."<sup>88</sup> Within the next few years, Mooser<sup>89</sup> and others obtained experimental evidence of differences produced in animals by inoculation with material from classical Old World and the milder New World typhus, and the etiological micro-organism, which had been seen by Mooser in infected cells, was isolated, characterized, and named *R. mooseri*. Maxcy's hypothesis was confirmed by Dyer in 1931 by the isolation of *R. mooseri* from fleas (*Xenopsylla cheopis*) collected from rats. By 1934, Zinsser<sup>90</sup> had clearly pointed out that Brill's disease was a form of recrudescent European louseborne typhus—a variety of epidemic typhus. This opinion expressed by Zinsser has been abundantly confirmed by the work of Murray and Snyder.<sup>91</sup>

<sup>87</sup> Maxcy, K. F.: An Epidemiological Study of Endemic Typhus (Brill's Disease) in the South-eastern United States, With Special Reference to Its Mode of Transmission. Pub. Health Rep. 41 (pt. 2) : 2967–2995, 24 Dec. 1926.

<sup>88</sup> Rozeboom, L. E.: Murine Typhus. In Preventive Medicine and Public Health (Rosenau), K. F. Maxcy, editor. 8th edition. New York: Appleton-Century-Crofts, Inc., 1956, pp. 428–434.

<sup>89</sup> Mooser, H.: Experiments Relating to the Pathology and the Etiology of Mexican Typhus (Tabardillo). 1. Clinical Course and Pathologic Anatomy of Tabardillo in Guinea Pigs. 2. Diplobacillus from the Proliferated Tunica Vaginalis of Guinea Pigs Reacting to Mexican Typhus. J. Infect. Dis. 43 : 241–260, 261–272, 1928.

<sup>90</sup> Zinsser, H.: Varieties of Typhus Virus and the Epidemiology of the American Form of European Typhus Fever (Brill's Disease). Am. J. Hyg. 20 : 513–532, November 1934.

<sup>91</sup> Murray, E. S., and Snyder, J. C.: Brill's Disease; Etiology. Am. J. Hyg. 53 : 22–32, January 1951.



During the 1930's, the agglutination of a suspension of *Proteus* OX-19 in the Weil-Felix reaction was identified within a recognized range of probability with infection with the murine type of typhus fever. Later, about 1944, specific serological reactions—agglutination and complement fixation reactions—became available by the use of specific rickettsial antigens obtained from cultures in yolk-sacs of embryonated hen's eggs.

At the time of the entry of the United States into World War II, there was a slightly current notion that the rickettsial agent of murine typhus could be changed into the rickettsial agent of epidemic typhus by passage through lice. During the war, Snyder and Wheeler<sup>92</sup> in the Cairo Laboratory of the U.S.A. Typhus Commission proved that the passage of *R. mooseri* through lice did not change it into *R. prowazeki*, and that murine flea-borne typhus did not change into epidemic louse-borne typhus.

In summary—

1. Murine typhus is primarily a disease enzootic in rodents, chiefly the wild roof rat (*Rattus alexandrinus*) and the brown rat (*Rattus norvegicus*), and, in addition, domestic rats, house mice, and the field mouse (*Mus musculus*, *Mus wagneri*, and *Peromyscus polionotus*). The important reservoir of *R. mooseri* is the commensal rat.

2. The disease is transmitted from rodent to rodent by a variety of their specialized arthropod ectoparasites, and from rat to man by the flea *X. cheopis*. It is not contagious from man to man. There is no need, therefore, for the isolation of patients or for restrictions upon the movements of contacts. Isolation precautions are not necessary in connection with the treatment of patients in hospitals.

3. Control measures are based upon the reduction of populations of rodents and fleas in communities.

4. The incubation period is from 10 to 14 days. The rash usually appears about the 4th day of the disease, and the symptoms last about 14 days. Convalescence may take a month or more. The case fatality rate is from 1 to 8 percent.

5. Murine typhus is essentially a disease of summer and fall, in contrast to epidemic louse-borne typhus which is usually a disease of the colder months of the year.

6. A moderate degree of immunity can be stimulated by injections of a vaccine composed of pure suspensions of *R. mooseri* and their soluble specific substance, made according to procedures already described in general for the preparation of typhus vaccine. Such a vaccine was not used in the Army during World War II, because, as already stated in Circular Letter No. 33 (p. 194): "The incidence of the disease is too low to warrant general vaccination. This procedure is not considered in places where the rat population can be controlled."

<sup>92</sup> Snyder, J. C., and Wheeler, C. M.: The Experimental Infection of the Human Body Louse, *Pediculus humanus corporis*, With Murine and Epidemic Louse-borne Typhus Strains. J. Exper. Med. 82: 1-20, July 1945.

## GEOGRAPHIC DISTRIBUTION OF MURINE TYPHUS

Fleaborne murine typhus fever occurs in all parts of the world as shown in map 3. Areas of special importance to the U.S. Army were:

1. The States in the southeastern United States; namely, North Carolina, Tennessee, South Carolina, Georgia, Alabama, Mississippi, Louisiana, Florida, and Texas. The 5-year attack rate per million population by States for reported cases of typhus fever, predominantly murine typhus, for the period 1941-45 is shown graphically in map 4.

2. North Africa and the Atlantic coast of Africa from Casablanca to Dakar.

3. Hawaii.

4. The Philippines, Japan, and Korea.

U.S. Army personnel were in contact with murine typhus in every area in which they were stationed during World War II.

## INCIDENCE OF MURINE TYPHUS IN THE ARMY

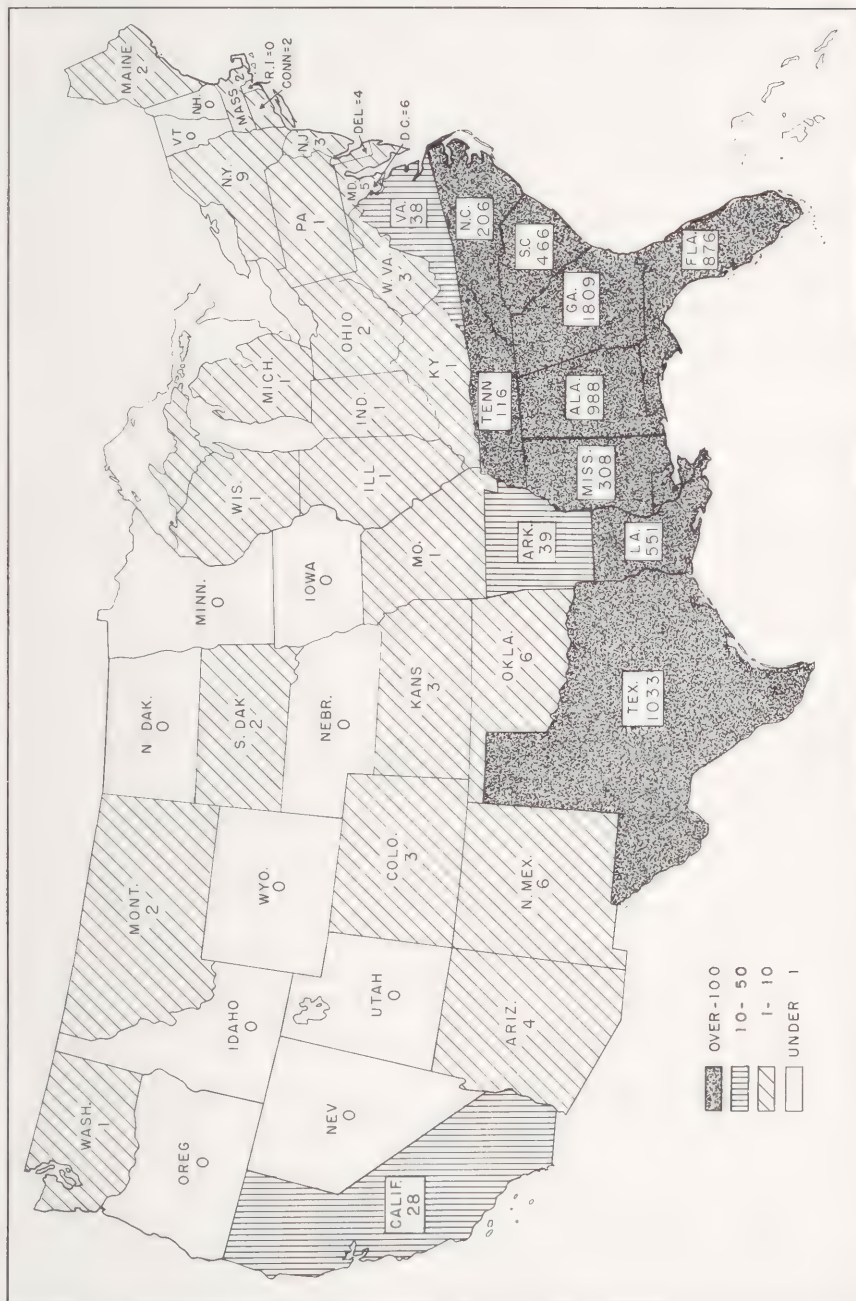
In view of this extensive exposure, it is not astonishing that there were 787 cases of murine fleaborne typhus in U.S. Army personnel during the period 1942-45, as shown in table 38, supplied by the Medical Statistics Division, Office of The Surgeon General. Of these reported cases, 497 occurred in the continental United States and 290 overseas.

The resultant noneffective rate was relatively insignificant. This daily rate per 1,000 average strength was less than 0.005.

As a cause of death, however, the so-called "mild" murine (endemic) fleaborne typhus fever was more lethal than the more dreaded epidemic (exanthematic) louseborne typhus. While there were no deaths from epidemic typhus among soldiers, there were 15 deaths (1 in the continental United States and 14 overseas) among the 787 cases of murine typhus, giving a case fatality rate of 1.9 percent.

It is the belief of the author, based upon hindsight, that these deaths could have been prevented by vaccination. The reasons why vaccination against murine typhus was not adopted are not entirely clear. The stated reason, as already quoted, was: "The incidence of the disease is too low to warrant general vaccination. This procedure is not considered in places where rat population can be controlled." The rat population was gradually brought under control in the southeastern and southern United States, but it could not be controlled in many places overseas. Perhaps it was assumed that epidemic typhus vaccination would confer a comfortable degree of immunity also against murine typhus. The British did not share this viewpoint. Their vaccine, based upon Craigie's work,<sup>93</sup> contained both *R. prowazeki* and *R. mooseri*. The review of the experience of the U.S. Army makes this author feel that it was a mistake not to have used a polyvalent vaccine to immunize against both epidemic and murine typhus.

<sup>93</sup> Craigie, J., Watson, D. W., Clark, E. M., and Malcomson, M. E.: Serological Relationships of Rickettsiae of Epidemic and Murine Typhus. *Canad. J. Research* 24 (Sec. E): 84-103, April 1946.



MAP 4.—Outline map of the United States showing reported cases of murine (endemic) fleaborne typhus, 1941–45, with 5-year attack rate per million population by States. (Courtesy of the Communicable Disease Center, Public Health Service, Department of Health, Education, and Welfare.)



TABLE 38.—*Incidence of murine (endemic) fleaborne typhus fever in the U.S. Army, by theater or area and year, 1942-45*

[Preliminary data based on sample tabulations of individual medical records]  
 [Rate expressed as number per annum per 1,000 average strength]

Theater or area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States .....	497	0.03	72	0.03	165	0.03	160	0.04	100	0.03
Overseas:										
Europe .....	5	0.00	0		0		5	0.00		0
Mediterranean <sup>1</sup> .....	12	.01	0		8	.02	4	.01		0
Middle East .....	9	.07	0		1	.02	8	.17		0
China-Burma-India .....	34	.08	0		7	.18	12	.07	15	.07
Southwest Pacific .....	87	.05	10	.14	39	.21	33	.06	5	.01
Central and South Pacific .....	123	.09	13	.09	65	.22	35	.08	10	.02
North America <sup>2</sup> .....	1	0.00	0		0		1	.01		0
Latin America .....	18	.05	3	.03	1	.01	4	.05	10	.14
Total overseas <sup>3</sup> .....	290	0.03	26	0.04	122	0.07	102	0.03	40	0.01
Total Army .....	787	0.03	98	0.03	287	0.04	262	0.03	140	0.02

<sup>1</sup> Includes North Africa.

<sup>2</sup> Includes Alaska and Iceland.

<sup>3</sup> Includes one admission on a transport in 1943.

NOTE.—Absolute zero is indicated by zero in the units column; 0.00 indicates a rate of more than zero but less than 0.005.

## PREVENTION AND CONTROL OF MURINE TYPHUS

The efforts to prevent and control murine typhus during World War II were exerted along two main lines; namely, (1) military and civilian lines in the United States and overseas, and (2) civilian lines within the United States. In both groups of activities, except for the segment of operations overseas, the collaboration between the Army Medical Service and the U.S. Public Health Service was all important. These two groups of activities will be discussed separately with the understanding that their coordination and mutual support was constant. The U.S. Public Health Service, the Preventive Medicine Service of the Office of The Surgeon General, and the U.S.A. Typhus Commission worked together for the common good.

### Military and Civilian Murine Typhus Control in the United States and Overseas

In January 1940, letters exchanged between the Secretary of War and the Federal Security Administrator revived the fine cooperation and support given by the U.S. Public Health Service to the Army, under the provisions of law and the Executive order (No. 2571) of 3 April 1917. The U.S. Public Health Service, operating under the authority of existing laws and using its own resources, collaborated with the Army in safeguarding the health of military personnel by suitable measures of extracantonment sanitation. This was

of particular importance for the control of murine typhus in connection with the concentration of troops in the South.

The U.S.A. Typhus Commission also had an obligation to assist in the prevention and control of murine typhus in the United States and elsewhere. After a number of conferences, the Executive Committee of the Commission decided that this problem within the continental limits of the United States had best be handled by the U.S. Public Health Service which was responsible under law.

As previously recorded, Colonel Plotz and his associates investigated an outbreak of murine typhus on Jamaica in July and August 1942. The surveys of the U.S.A. Typhus Commission in North Africa, in the Middle East, and in the Pacific Ocean Areas provided a large amount of useful information about the prevalence of murine typhus in those regions. All of this contributed to a sense of security with regard to this disease, and perhaps to an unjustifiable disregard of its lethal potentiality.

Circular Letter No. 33 (p. 194) on the subject of the treatment and control of certain tropical diseases dealt with endemic murine typhus. This was a useful statement, composed in Preventive Medicine Service, but it contained some errors. It gave, however, sufficient emphasis to the rat-flea-man pathway of the transmission of murine typhus.

The rodent control program was specified in several technical bulletins in 1945 and has been fully described by Colonel Hardenbergh<sup>94</sup> and his associates. This program, which included control of fleas, gave directions for ratproofing of buildings and for trapping and poisoning rats. It advised that runways of rats be dusted with DDT powder to kill fleas. This proved to be an effective measure of control. These measures were applied with success in Georgia and Texas, in 1943 and 1944, where soldiers were exposed to murine typhus when they visited towns near their encampments.

Probably the first experiments on the control of murine typhus by dusting rat runs with DDT to kill fleas were made under military auspices in North Africa in 1943-44. This logical plan of attack was developed with great success by the U.S. Public Health Service.

At this point, brief mention will be made of the problems of murine typhus in the Central, South, and Southwest Pacific Areas, in the Philippines, and in Japan and Korea.

In the Hawaiian Islands, murine typhus had been prevalent for many years.<sup>95</sup> During the period 1942-45, 123 cases occurred among U.S. Army

<sup>94</sup>(1) War Department Technical Bulletin (TB MED) 144, April 1945. (2) Hardenbergh, William A., and Gilbert, Joseph J.: Rodent Control. In Medical Department, United States Army. Preventive Medicine in World War II. Volume II. Environmental Hygiene. Washington: U.S. Government Printing Office, 1955, pp. 233-249. (3) See footnote 20(2), p. 190.

<sup>95</sup>(1) Martin, Walter B., and Young, Charles T.: Murine Typhus in the Hawaiian Islands. In Report on Activities of the Medical Consultants, Middle Pacific Area, pp. 173-174. [Official record.] Also, in History of Preventive Medicine, U.S. Army Forces, Middle Pacific, 1941-45, p. 185. [Official record.] (2) Wilbar, C. L., Jr.: Annual Report of the Board of Health, Territory of Hawaii, for the Fiscal Year 1944, ending on 30 June 1944, pp. 10, 41, 45, and 55.

personnel stationed in the Central and South Pacific Areas. In addition, there were 87 cases among soldiers in the Southwest Pacific Area.

The occurrence of murine typhus in the Philippine Islands had been questionable, although DeRoda had reported its probable occurrence in 1937. Its presence in Manila and on Mindanao was definitely proved by Woodward, Philip, and Loranger<sup>96</sup> in 1945. This finding added more substance to the opinion that "murine typhus fever is undoubtedly the most widespread of all the rickettsial group of infections, among which, fortunately, it may be classified as the more benign."

As previously noted (p. 256), epidemic typhus was widespread in Japan and Korea in 1945-46. In discussing the incidence of typhus in those countries during that year, it was recognized that diagnoses were specifically confirmed in only a few cases among the thousands of patients. It was well known that murine typhus was occurring in Japan and Korea at this time. It has been estimated that 20 percent of typhus in those countries was murine typhus—but who knows?

### Civilian Control of Murine Typhus in the United States

As the largest encampments, posts, training areas, and maneuver regions of the U.S. Army became located in the southeastern and southern States (Tennessee, North Carolina, Texas, Louisiana, Mississippi, Alabama, Georgia, South Carolina, and Florida), the prevalence of murine typhus in these States assumed a military importance equal to its civilian importance as a cause of sickness and death. Through the cordial cooperation between the U.S. Public Health Service and the Army, effective operations for the control of the disease in this area were carried out (and are being continued) with mutual advantage to military and civilian populations.

A fitting conclusion to this chapter is a brief account of the extraordinary control over murine typhus which has been achieved in this area by the U.S. Public Health Service.

The results of intensively applied programs for rodent control and flea control are shown in charts 16 and 17 which portray graphically the numbers of reported cases of typhus fever, predominantly murine, in the United States from 1931-50, and 1941-56, respectively. The situation during the war period is shown by State in map 4. Chart 17 shows the great decrease in reported cases of murine typhus that has occurred since the start of the DDT control program in 1945, when about 5,000 cases were reported, to 1956, when the reported cases were less than 100.

Perhaps it is well to close this section on a modest note by quoting from a letter of 27 July 1957 from Dr. Alexander D. Langmuir, Chief of the Epi-

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<sup>96</sup> Woodward, T. E., Philip, C. B., and Loranger, G. L.: Endemic Typhus in Manila, P.I. Report of Cases and Identification of the Murine Rickettsial Agent in Domestic Rats by Complement Fixation. *J. Infect. Dis.* 78: 167-172, March-April 1946.

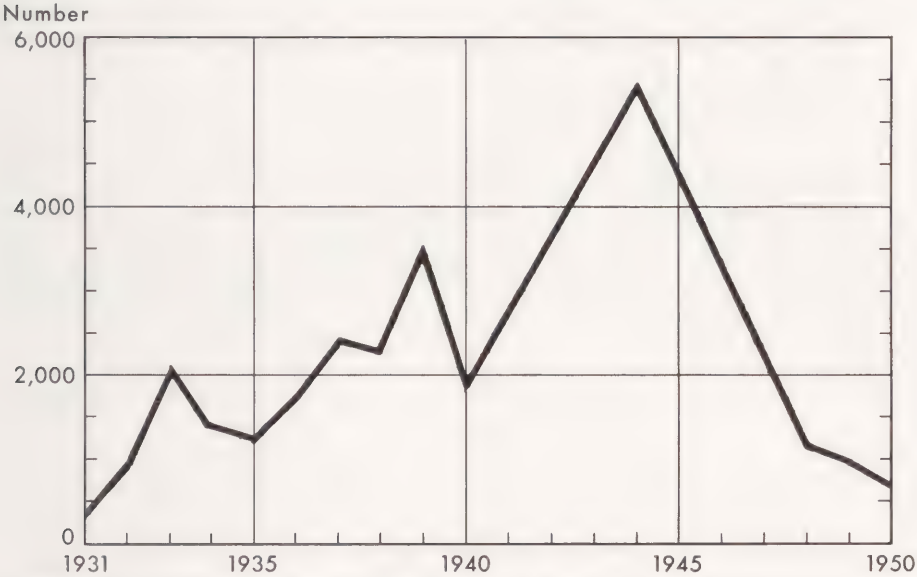


demiology Branch of the Communicable Disease Center, U.S. Public Health Service, at Atlanta. He wrote to the author of this chapter:

Many of us here are very skeptical that the control program was really the important undertaking. The intensive rat control program in some of the larger cities was of real value. The spraying of rat runs with DDT may or may not have been of great importance. We now have essentially no typhus control program, and yet there is no suggestion of a resurgence of the disease more than five years after the last DDT dusting has been done. Advancement in the standard of living and generally better housing and community sanitation have probably removed the contact of rats with humans.

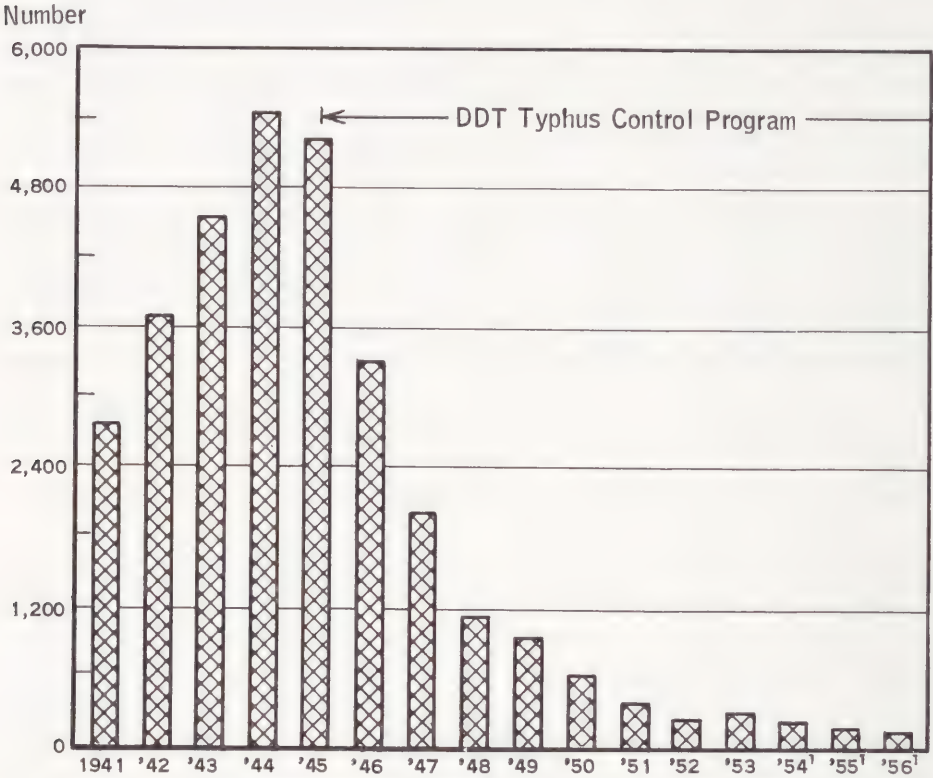
There are, indeed, mysteries in the ways of both epidemic and murine typhus. Perhaps there may be a resurgence of both, since both lice and fleas have become resistant to several insecticides on which dependence had been placed. At the end of World War II, however, conquest of both forms of typhus seemed to be unconditionally accomplished.

CHART 16.—*Murine, fleaborne, typhus in the United States; total reported cases, 1931–50, showing the large increase that occurred during the war years, 1941–44*



Source: U.S. Department of Health, Education and Welfare, Public Health Service, National Office of Vital Statistics. Vital Statistics-Special Reports, National Summaries, vol. 37, No. 9, 15 June 1953, Reported Incidence of Selected Notifiable Diseases, United States, Each Division and State, 1920–50.

CHART 17.—*Annual total of reported murine typhus cases in the United States, 1941–56, showing the great reduction in incidence since the initiation in 1945 of the DDT typhus control program directed against rat fleas*



(Chart courtesy of the Communicable Disease Center, U.S. Public Health Service, Department of Health, Education, and Welfare.)

<sup>1</sup> Tentative.

## CHAPTER XI

# Scrub Typhus and Scrub Itch

*Cornelius B. Philip, M.S., Ph. D., Sc. D.*

## INTRODUCTION

"Scrub Typhus Fever is a serious disease prevalent in the Asiatic-Pacific Area. In some operations, it has disabled more men than has enemy action. Because of its importance and because of expanding military activity in this area, all individuals should know how to protect themselves from it." So reads the opening statement of an Army Ground Forces headquarters' directive, dated 9 November 1944, to various units of troops staging in the United States as part of the preparation for the final assault on Japan.

Fortunately, the early capitulation of Japan obviated the need for completion of antimite preparations, after reoccupation of the Philippines, and for issuance of supplies of improved repellent. Indoctrination of troops was already underway, based on lessons gleaned from experience with scrub typhus or tsutsugamushi disease in previous campaigns. This experience will be discussed hereafter as three major episodes, one each in SWPA (Southwest Pacific Area) and SPA (South Pacific Area) and one in CBI (China-Burma-India) theater (map 5). Postwar information has considerably expanded our knowledge of the geographic distribution of the disease, particularly in India, Thailand, south China, the Andaman Islands, and southern Honshu, Japan.<sup>1</sup>

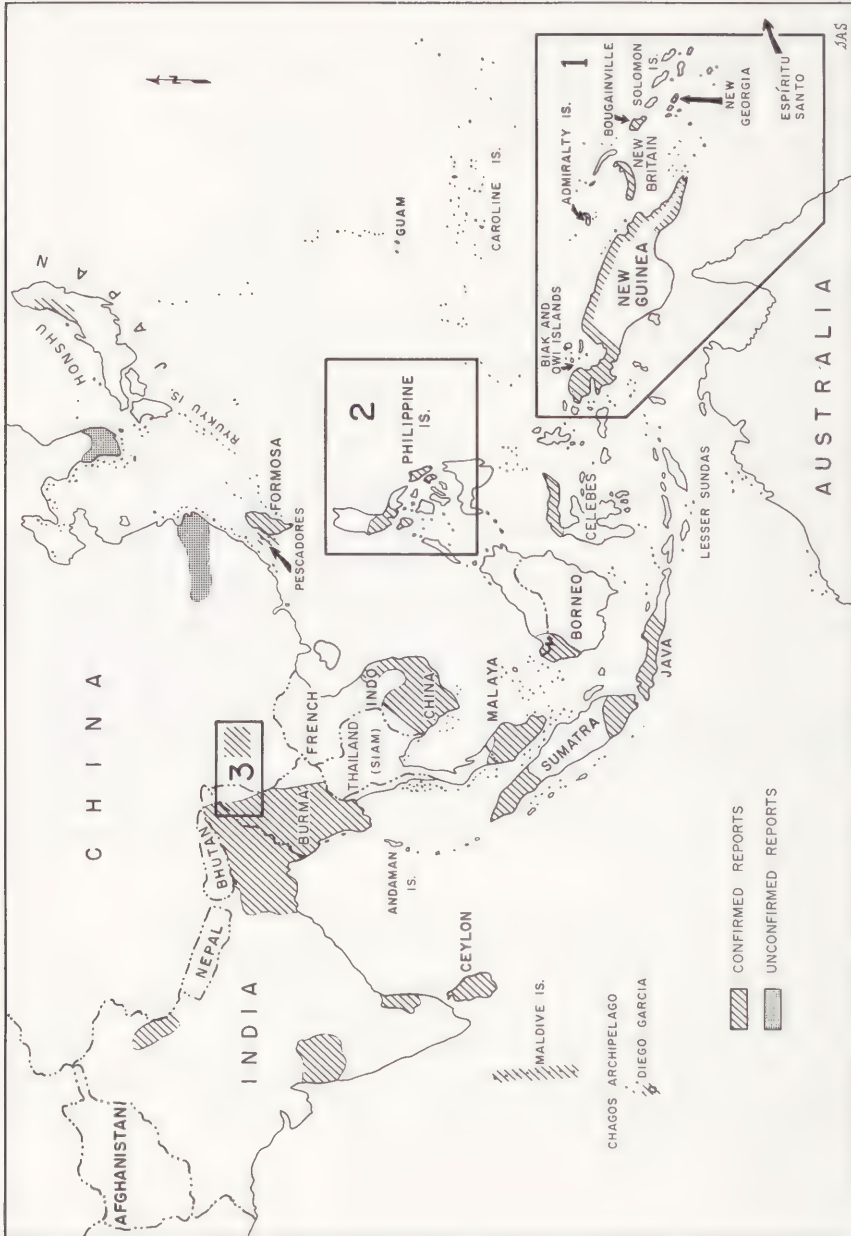
The unopposed occupation of the three notoriously endemic prefectures—Akita, Yamagata, and Niigata in northwest Honshu—in the fall of 1945 by units of the Sixth U.S. Army (11th Airborne and 27th Infantry Divisions) reduced the necessity for field exposure in these areas. This, coupled with the lateness of the season, prevented infections in military personnel during the 1945 administrative operation in Japan.<sup>2</sup> Though there was some apprehension regarding the disease before the earlier Okinawa invasion, no cases of scrub typhus were encountered during that operation.

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<sup>1</sup> Bell, E. J., and Philip, C. B.: The Human Rickettsioses. *Ann. Rev. Microbiol.* 6: 91–118, 1952.

<sup>2</sup> Philip, C. B.: Observations on Tsutsugamushi Disease (Mite-borne or Scrub Typhus) in Northwest Honshu Island, Japan, in the Fall of 1945. II. Systematic Comment on the Japanese Vole-mites. *Am. J. Hyg.* 46: 60–65, July 1947.





MAP 5.—The areas in which occurred the three major episodes of scrub typhus in U.S. Army Forces. These areas are shown in relation to present known distribution of the disease in the Asiatic-Pacific region. (Blake, Maxcy, Sadusk, Khols, and Bell. *Am. J. Hyg.* 41: 243-373, May 1945.)

### Early History

The prewar documentation of scrub typhus in the various endemic areas of the region is extensive and has been reviewed many times.<sup>3</sup> A Chinese writing in the 16th century associated minute red "sand lice" along certain rivers with illnesses in natives of south China. As early as 1810 in Akita Prefecture, Honshu, Japan, a similar illness, "tsutsuga," was known and was linked here and in Niigata with "tsutsuga-mushi" or disease mites long before scientific acceptance and proof of mite transmission of this disease. This, incidentally, was almost a century before the human louse was suspected of transmission of typhus fever, the other centuries-old, related scourge in Europe.

Discovery of somewhat similar maladies came much later in Formosa, Malaysia, various South Pacific islands, and Australia. They were usually given colloquial names until, within the past two decades, laboratory procedures confirmed the suspicion that, in spite of some clinical differences, these were the same as the more virulent tsutsugamushi disease in Japan. Even most experienced Japanese medical officers during World II, faced with such casualties in Burma and elsewhere, would not diagnose it as the same disease (see pp. 344-347).

Control measures, until the development of modern repellents and acaricides, were crude and rather ineffective in endemic areas, especially where intensive, continuous cultivation could not be practiced. As late as 1945, some Japanese farmers in Niigata wore customary one-piece clothing and leggings to try to restrict mite attack when going into infested locations.

Prewar knowledge of geographic variations in the epidemiology and ecology of the disease was greatly extended during military operations. The term "scrub typhus" originated in Malaya in contrast to so-called shop or urban typhus and was the designation adopted for purposes of military records because of widespread usage in the Southwest Pacific region.

For intelligent subsequent presentation of epidemiological features of the disease in the U.S. Army experience, it is desirable to define the disease and to provide statistics on the incidence in troops in the various theaters.

### Definition and Clinical Characteristics

Scrub typhus is a specific febrile infection due to a rickettsial agent transmitted by certain species of chigger mites which habitually infest local small animals, particularly nondomestic rats, and some ground-frequenting birds. The usual clinical characteristics of cutaneous eruption, febrile course of about 2 weeks, lymphadenopathy, and often a primary lesion or eschar at the site

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<sup>3</sup> Blake, F. G., Maxey, K. F., Sadusk, J. F., Jr., Kohls, G. M., and Bell, E. J.: Studies on Tsutsugamushi Disease (Scrub Typhus Mite-borne Typhus) in New Guinea and Adjacent Islands: Epidemiology, Clinical Observations, and Etiology in the Dobodura Area. *Am. J. Hyg.* 41: 243-373, May 1945.

of bite by the vector, in two or more respects resemble other typhuslike rickettsioses. A further point of resemblance is the usual development in early convalescence of a positive Weil-Felix reaction, though the agglutinins are peculiar for the mutant OX-K strain of the *Proteus* bacillus.

The clinical, pathologic, and therapeutic features have been summarized by Zarafonetis and Baker.<sup>4</sup> The proportionate occurrence of these clinical symptoms varied in different episodes, but lymphadenopathy was the most consistent; it occurred even in ambulatory, nonhospitalized patients as confirmed by subsequent serologic testing of individuals; 97 percent of 1,255 cases in the Owi-Biak epidemic had at least regional glandular involvement draining the site of infection. Rash varied from 70 percent to "almost all" in various outbreaks,<sup>5</sup> and the eschar from 85 percent to only 11.<sup>6</sup> No relationship could be detected between the variations in virulence in different areas.

### THE INCIDENCE OF SCRUB TYPHUS IN THE U.S. ARMY

The total number of cases of scrub typhus in U.S. Army Forces in all areas from March 1942 through December 1945 was estimated at 6,717 as reported by the statistical health reports in the Surgeon General's Office and compiled by Dr. Philip E. Sartwell. Comparison with incidence in other armed forces by year and locality is given in table 39. The overall Army figures have since been revised and are provided in tables 40 and 41.

Table 42 gives a breakdown of cases by area and theater—SWPA, 5,718; SPA, 32; and CBI, 967.<sup>7</sup> The 5,718 SWPA cases included 284 in troops during reoccupation of the Philippines from November 1944 through December 1945, and 28 in Australia in those two complete years. Separate data are not available for Australia for 1942 and 1943. It is likely that two known cases of murine typhus in the Philippines and a few in Australia are included in the totals because of the methods of reporting all types of typhus as a combined figure in the statistical health report. Similarly, in the total of 967 cases for the CBI, separate reporting of "e" (epidemic) or endemic (murine) typhus from "s" (scrub) typhus was not initiated until March 1945. The figures have

<sup>4</sup> Zarafonetis, Chris J. D., and Baker, Myles P.: Scrub Typhus. In Medical Department, United States Army. Internal Medicine in World War II. Volume II. Infectious Diseases. Washington: U.S. Government Printing Office, 1963, pp. 111-142.

<sup>5</sup> Philip, C. B.: Tsutsugamushi Disease (Scrub Typhus) in World War II. J. Parasitol. 34: 169-191, June 1948.

<sup>6</sup> Irons, E. N., and Armstrong, H. E.: Scrub Typhus in Dutch New Guinea. Ann. Int. Med. 26: 201-220, February 1947.

<sup>7</sup> Some dozen cases have been reported from the United States during the war for various reasons. In at least one instance, a case developed en route to the United States by plane and was first reported from a hospital at Camp Kilmer, N.J., in August 1945. Another case, reported as "an aviator," was hospitalized in San Francisco, Calif., 7 days after arrival with clinical symptoms and positive OX-K serology after exposure in a South Pacific island. Such reports were corrected as to locality as soon as they were received by the Medical Statistics Division, Office of The Surgeon General.



TABLE 39.—*Cases and deaths due to scrub typhus in U.S. and Allied military forces, during World War II, 1942–45, in selected areas, by theater or command*

Theater or command	1942		1943		1944		1945		Total	
	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths
New Guinea and adjacent islands:										
Australian Army---	186	40	1,870	112	602	78	181	27	2,839	257
U.S. Army-----	33	0	941	51	4,383	165	80	19	5,437	235
U.S. Navy-----	0	0	47	3	360	20	170	3	487	26
Philippines:										
U.S. Army-----	0	0	0	0	13	0	271	10	284	10
U.S. Navy-----	0	0	0	0	36	1	62	1	98	2
Remainder Southwest Pacific and South Pacific including Australia:										
Australian Army---	2	1	160	8	152	2	31	0	345	11
Australian Navy---	0	0	1	0	3	0	0	0	4	0
U.S. Army-----	1	0	0	0	26	0	2	0	29	0
Southeast Asia: <sup>1</sup>										
U.S. Army-----	0	0	56	0	610	28	301	30	967	58
Chinese Army-----	0	0	17	1	202	26	130	13	349	40
British-Indian Army-----	+	+	537	(2)	3,801	(2)	1,062	(2)	5,400	(2)
Grand total-----	222	41	3,629	175	10,188	320	2,290	103	16,239	639

<sup>1</sup> Including Assam but excluding the remainder of India, data for which are not available for comparative tabulation. All-India total British cases from various sources for 1942–45, 420 ± cases; Ceylon, 1942–44, 799 cases; Maldives Islands and Diego Garcia, 1942–44, at least 726 cases, plus approximately 79 cases (Navy or Army unknown, but Hayakawa (see addendum, footnote 88, p. 354) tabulates 5 cases in Japanese troops at “Car Nicobar Island”).

<sup>2</sup> Data not supplied.

Source: Compiled by the author in correspondence with statistical agencies of various armed services listed.

not been corrected to eliminate such known cases of endemic typhus which were included in the statistical health reports subsequent to that date (together with about 1,250 additional cases eliminated in the revised statistics, see tables 40 and 41), for consistency with other historical data. Of the 967 CBI cases, at least 125 were reported from China, many of which were probably endemic typhus.<sup>8</sup> It is not known how many were actually scrub typhus, nor how many came over from Burma during their incubation periods, as discussed later.

The figures of 1,000 per year rates given in table 43 show totals for the 4 years, 1942–45, of 3.34 and 2.23 for the SWPA and CBI, respectively. The highest rate of 9.75 for SWPA, other than Australia and the Philippines in 1944, is due chiefly to two major epidemics encountered on the Ow-Biak and Sansapor beachheads in New Guinea (p. 285).

<sup>8</sup> Verbal report to this author by Medical Consultant, Chief Surgeon's Office, China Theater, 25 May 1946.

TABLE 40.—*Incidence (total cases) of scrub typhus in the U.S. Army, by theater and year, 1942-45*

[Preliminary data based on sample tabulations of individual medical records]  
 [Rate expressed as number per annum per 1,000 average strength]

Theater or area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States.....	5	0.00	-----	0.0	-----	0.0	-----	0.0	5	0.0
Overseas:										
Europe.....	0		0		0		0		0	
Mediterranean <sup>1</sup> .....	0		0		0		0		0	
Middle East.....	0		0		0		0		0	
China-Burma-India.....	804	1.83	0		11	0.28	543	3.22	250	1.13
Southwest Pacific.....	4,459	2.43	35	.49	722	3.80	3,437	6.37	265	.26
Central and South Pacific.....	171	.14	1	.01	10	.03	150	.34	10	.02
North America <sup>2</sup> .....	0		0		0		0		0	
Latin America.....	0		0		0		0		0	
Total overseas <sup>3</sup> .....	5,436	0.51	36	0.06	745	0.44	4,130	1.08	530	0.11
Total Army.....	5,441	0.21	36	0.01	745	0.11	4,130	0.53	525	0.07

<sup>1</sup> Includes North Africa.

<sup>2</sup> Includes Alaska and Iceland.

<sup>3</sup> Includes admissions on transports.

NOTE.—Absolute zero is indicated by zero in the units column; 0.0 indicates a rate of more than zero but less than 0.05 and 0.00 a rate more than zero but less than 0.005.

TABLE 41.—*Deaths due to scrub typhus in the U.S. Army, by theater of admission and year of death, 1942-45*

[Preliminary data based on sample tabulations of individual medical records]  
 [Rate expressed as number per annum per 100,000 average strength]

Theater or area	1942-45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States.....	1	0.01	-----	0.0	-----	0.0	-----	0.0	1	0.03
Overseas:										
Europe.....	0		0		0		0		0	
Mediterranean <sup>1</sup> .....	0		0		0		0		0	
Middle East.....	0		0		0		0		0	
China-Burma-India.....	64	14.60	0		0		33	19.56	31	14.00
Southwest Pacific.....	214	11.65	0		49	10.18	143	26.89	20	1.93
Central and South Pacific.....	3	.24	0		0		1	.23	2	.53
North America <sup>2</sup> .....	0		0		0		0		0	
Latin America.....	0		0		0		0		0	
Total overseas <sup>3</sup> .....	282	2.63	0		49	2.90	180	4.71	53	1.14
Total Army.....	283	1.11	0		49	0.71	180	2.31	54	0.71

<sup>1</sup> Includes North Africa.

<sup>2</sup> Includes Alaska and Iceland.

<sup>3</sup> Includes one death among transport admissions in 1944.

NOTE.—Absolute zero is indicated by zero in the units column; 0.0 indicates a rate of more than zero but less than 0.05.

TABLE 42.—Case incidence of scrub typhus fever in U.S. Army troops, by month, 1942-45, and by area and theater of admission <sup>1</sup>

[Preliminary data based on summaries of statistical health reports]

Month and year	Southwest Pacific Area				South Pacific Area	China-Burma-India theater				
	Total	Australia	Philippines	Other		Total	Burma-India	China		
1942										
March.....	1	1								
July.....	1									
August.....	2									
September.....	8									
October.....	7									
November.....	7									
December.....	8									
Total.....	34	1								
1943										
January.....	92				1	1				
February.....	62									
March.....	45									
April.....	55									
May.....	64									
June.....	79									
July.....	83									
August.....	81									
September.....	95									
October.....	93									
November.....	67									
December.....	119									
Total.....	935				6	56				
1944										
January.....	75	1		74	2	10				
February.....	104	6		98	3	21				
March.....	184	2		182	3	2				
April.....	75	1		74	5	37				
May.....	130			130	8	67				
June.....	212	11		201	3	64				
July.....	647	2		645	2	45				
August.....	1,759			1,759		38				
September.....	757	2		755		45				
October.....	251	1		250		103				
November.....	113			1	112	89			81	8
December.....	89			12	77	89			84	5
Total.....	4,396	26	13	4,357	26	610	165	13		

See footnotes at end of table.



TABLE 42.—*Case incidence of scrub typhus fever in U.S. Army troops, by month, 1942-45, and by area and theater of admission—Continued*

Month and year	Southwest Pacific Area				South Pacific Area	China-Burma-India theater		
	Total	Australia	Philippines	Other		Total	Burma-India	China
1945								
January-----	100	2	86	12		108	102	6
February-----	66		49	17		33	27	6
March-----	45		23	22		26	6	20
April-----	32		27	5		14	1	13
May-----	15		13	2		10	1	9
June-----	43		40	3		31	10	21
July-----	20		18	2		28	16	12
August-----	11		10	1		19	8	11
September-----	3	( <sup>2</sup> )	2	( <sup>2</sup> )		14	8	6
October-----	11	( <sup>2</sup> )	( <sup>2</sup> )	( <sup>2</sup> )		11	8	3
November-----	2	( <sup>2</sup> )	1	( <sup>2</sup> )		5	2	3
December-----	5	( <sup>2</sup> )	2	( <sup>2</sup> )		2	0	2
Total-----	353	2	271	64	0	<sup>3</sup> 301	169	112
Grand total-----	5, 718				32	<sup>3</sup> 967		

<sup>1</sup> See tables 40 and 41 for amended figures (1957).<sup>2</sup> Unreported though troops in area.<sup>3</sup> Not corrected to exclude 128 known cases of endemic (murine) and epidemic typhus.

The figures in both tables 42 and 43 provide columns for the South Pacific Area to include a few cases<sup>9</sup> which occurred in the U.S. Army Forces in the islands of Espíritu Santo, New Georgia, and Bougainville before the last was transferred from the jurisdiction of the South Pacific to Southwest Pacific Area in August 1944.<sup>10</sup> Although indeterminate reference has been made to a focus of the disease on one of the Treasury group of islands, south of Bougainville, which was occupied chiefly by Naval personnel, other reports indicate only the occurrence of severe, mite-caused, scrub itch. Almost 80 percent of

<sup>9</sup> Because it had been suggested that a large proportion of the 176 total (1942-45) typhus cases in the Central Pacific Area (including the South Pacific Area) forces were probably scrub typhus, attention is called to the report of 106 cases of murine typhus in the Hawaiian Islands for 1943-44. (Martin, W. B., and Young, C. T.: Report on Activities of the Medical Consultants, Middle Pacific Area. Murine Typhus in the Hawaiian Islands, pp. 173-174. [Official record.]). More probably occurred in 1945. On the other hand, while 32 cases of scrub typhus are reported officially for SPA by statistical health reports (see table 42), 65 and "over 70" cases are specifically mentioned in individual reports for the island of Bougainville alone in SPA.

<sup>10</sup> Essential Technical Medical Data, Headquarters, South Pacific Base Command, U.S. Army, for August 1944, dated 1 Sept. 1944. (2) Letter, Capt. Louis G. Welt, MC, Malariologist, Headquarters, Malaria and Epidemic Control, Americal Division, to Chief Malariologist, Headquarters, U.S. Army Forces in the Far East, 28 Oct. 1944, subject: Report on Effectiveness of Dimethyl Phthalate-Impregnated Clothing in Preventing Scrub Typhus. (3) Entomological News Letter No. 7, Headquarters, Malaria and Epidemic Control, South Pacific Area, Navy 140, 1 Dec. 1943. (4) Essential Technical Medical Data, Headquarters, XIV Corps, U.S. Army, for August 1944, dated 13 Sept. 1944.

TABLE 43.—*Admission rates of scrub typhus in U.S. Army troops, by month, 1942-45, and by theater of admission* <sup>1</sup>

[Preliminary data based on summaries of statistical health reports]  
[Rate expressed as number of cases per annum per 1,000 average strength]

Month and year	Southwest Pacific Area				South Pacific Area	China-Burma-India theater		
	Total	Australia	Philippines	Other		Total	Burma-India	China
1942								
March.....	0. 96							
July.....	. 12							
August.....	. 27							
September.....	1. 06							
October.....	. 71							
November.....	. 87							
December.....	. 96							
Total.....	0. 51							
1943								
January.....	8. 89					0. 56		
February.....	6. 99					0		
March.....	4. 55					0		
April.....	4. 12					0		
May.....	5. 62					0		
June.....	6. 26					0		
July.....	4. 55					0		
August.....	5. 12				0. 09	. 30		
September.....	4. 08					1. 94		
October.....	4. 64					. 28		
November.....	3. 06					. 66		
December.....	4. 04				. 33	4. 41		
Total.....	4. 79				0. 04	1. 22		
1944								
January.....	3. 13	0. 12		4. 66	0. 12	1. 33		
February.....	4. 26	. 85		5. 65	. 17	2. 59		
March.....	5. 19	. 24		6. 68	. 15	. 17		
April.....	2. 28	. 17		2. 72	. 28	3. 60		
May.....	3. 70	0		4. 36	. 46	5. 62		
June.....	4. 12	1. 72		4. 46	. 16	4. 10		
July.....	13. 40	. 42		14. 84	. 20	3. 46		
August.....	34. 56	0		37. 59	0	2. 80		
September.....	11. 70	. 43		12. 58	0	2. 53		
October.....	4. 60	. 29		4. 88	0	7. 12		
November.....	1. 92	0	0. 06	2. 82	0	5. 77	5. 98	4. 26
December.....	1. 21	0	. 42	1. 78	0	4. 44	4. 79	1. 99
Total.....	7. 93	0. 41		9. 75		3. 82		

See footnotes at end of table.

TABLE 43.—*Admission rates of scrub typhus in U.S. Army troops, by month, 1942-45, and by theater of admission*<sup>1</sup>—Continued

Month and year	Southwest Pacific Area				South Pacific Area	China-Burma-India theater		
	Total	Australia	Philippines	Other		Total	Burma-India	China
1945								
January-----	1. 66	1. 01	2. 67	. 46		6. 17	6. 71	2. 60
February-----	1. 10	0	1. 36	. 76		1. 77	1. 69	2. 24
March-----	. 62	0	. 49	. 94		1. 08	. 29	5. 60
April-----	. 54	0	. 63	. 33		. 74	. 06	4. 26
May-----	. 25	0	. 28	. 15		. 55	. 07	2. 60
June-----	. 56	0	. 64	. 22		1. 31	. 54	4. 13
July-----	. 31	0	. 32	. 29		1. 49	1. 13	2. 63
August-----	. 11	0	. 13	. 01		. 82	. 47	1. 78
September-----	. 04	(2)	. 04	(2)		. 75	. 59	1. 19
October-----	. 12	(2)	(2)	(2)		. 65	. 60	. 84
November-----	. 02	(2)	. 02	(2)		. 30	. 14	1. 12
December-----	. 08	(2)	. 01	(2)		. 27		1. 92
Total-----	0. 39	(2)	. 48	(2)		1. 35	1. 06	2. 59
Grand total-----	3. 34					2. 23		

<sup>1</sup> See tables 40 and 41 for amended figures (1957).<sup>2</sup> Unreported though troops in area.

the sickbay calls there were due to lesions initiated by these mite bites. Only three cases of scrub typhus were reported from Espíritu Santo. They were members of an engineering construction battalion engaged in clearing brush during the 18 to 24 days prior to the onset of their illness. Characteristic symptoms were observed, and all developed positive OX-K agglutinins as checked in two laboratories. This constituted the farthest eastern locality in which scrub typhus was encountered. No other reports of the disease were forthcoming from any of the islands in the Central or South Pacific Areas.

### Scrub Typhus in New Guinea and Adjacent Areas

The Essential Technical Medical Data report from the Southwest Pacific Area for September 1944, dated 5 October 1944, summarized the experience with scrub typhus up to that time as follows:

The first cases of scrub typhus in this theater were noticed late in 1942 as troops began to move into New Guinea. During the last 5 months of that year, the total of 32 cases were reported, but in January 1943, the number rose to 92 for a single month. Thereafter, the rate remains about the same with a total of 925 cases being reported in 1943, and 438 cases in the first 6 months of 1944. At that time, task forces moving into Dutch New Guinea were struck with the disease in epidemic form and twice as



many cases occurred in the ensuing 10 weeks as had occurred in the previous 23 months, a total of 2,803 cases so reported.

Up to that time, minor foci were encountered in northern Queensland, Australia, and at Port Moresby and Milne Bay in New Guinea, while more important outbreaks occurred in the Oro Bay-Dobodura, Markham Valley, and Goodenough Island areas, as well as in Cape Gloucester in New Britain.<sup>11</sup> "The disease was continuously encountered as the military operations moved northward along the coast to Salamaua, Wau, Lae, Nadzab, and Finschhafen \* \* \* " <sup>12</sup> during this earlier period, but these episodes all remained of relatively minor epidemiological significance.

The mortality rate is not significant in a military sense. However, in the mortality rate from all diseases in the theater, typhus deaths account for 30 to 50 percent. The mean case fatality rate remains low \* \* \* .<sup>13</sup>

In comparison with the overall incidence and rate in SWPA, given in tables 42 and 43, a summary of the incidence, mortality rate, and case fatality rate is shown in table 44 for the period, August 1942 to December 1943, based on strength only of troops in bases north of Australia.<sup>14</sup> These figures are consequently higher but give a better picture of noneffectiveness due to scrub typhus in foci encountered in forward areas of operation.

The experiences of individual units were sometimes more serious:

In one unit, with a strength of a 1,565, that had an average exposure period of 11.74 days in the Markham Valley, 37 cases of scrub typhus developed \* \* \*. The admission rate for the period exposed was 73.5 per 1,000 per annum and the average length of stay in the hospital was in excess of 70 days. Thirty-three were evacuated to the mainland in which one death occurred (the Commanding Officer of Company F).<sup>15</sup>

The two most serious episodes in the entire Army experience in any area followed almost immediately the landings on Owi-Biak and Sansapor beach-heads in Netherlands New Guinea between June and August 1944. These two outbreaks provided about 2,000 cases.<sup>16</sup> By the end of 1944, there were 2,500 cases in the two areas. Although the case fatality rate was very low (about 2 percent), the loss of time from duty represents a major military handicap. In many patients, the fever lasted for more than 20 days. About 5 percent of the cases were seriously ill.

<sup>11</sup> Essential Technical Medical Data, Southwest Pacific Area, U.S. Army, for February 1944, dated 3 Mar. 1944.

<sup>12</sup> See footnote 3, p. 277.

<sup>13</sup> Report, Col. Maurice C. Pincoffs, MC, Chief Consultant, to the Chief Surgeon. U.S. Army Forces in the Far East, 1 Feb. 1944, subject: Report on Scrub Typhus Fever.

<sup>14</sup> Essential Technical Medical Data, Southwest Pacific Area, U.S. Army, for September, dated 5 Oct. 1944.

<sup>15</sup> (1) See footnote 11. (2) Medical data on this disease are presented in other reports, but a minimum of such data are also included in this section to emphasize such epidemiological features as differences in virulence in different outbreaks, and the potential military cost in time lost to provide a basis, if desired, for contrast with other infections such as dengue.

<sup>16</sup> (1) Philip, C. B., and Woodward, T. E.: Tsutsugamushi Disease (Scrub-Typhus or Mite-borne Typhus) in the Philippine Islands During American Reoccupation in 1944-45. II. Observations on Trombiculid Mites. J. Parasitol. 32: 502-513, October 1946. (2) Verbal reports to the author from Lt. H. Wharton, USNR, who identified the mites concerned.

TABLE 44.—*Incidence and mortality due to scrub typhus fever in U.S. Army troops in bases north of Australia, August 1942–December 1943, by month*

[Incidence rate expressed as number of cases per 1,000 average strength]  
[Mortality rate expressed as number of deaths per 1,000 average strength]

Month and year	Cases	Deaths	Incidence rate	Mortality rate	Case fatality ratio (percent)	Strength
<i>1942</i>						
August-----	2	-----	5. 02	-----	-----	5, 174
September-----	8	-----	10. 47	-----	-----	9, 933
October-----	7	-----	3. 55	-----	-----	20, 474
November-----	7	-----	3. 08	-----	-----	29, 457
December-----	8	-----	2. 96	-----	-----	35, 044
<i>1943</i>						
January-----	92	<sup>1</sup> 4	22. 80	1	4. 3	41, 954
February-----	62	1	25. 73	. 41	1. 6	31, 315
March-----	45	<sup>1</sup> 5	12. 91	1. 43	11. 1	45, 291
April-----	55	2	10. 77	. 39	3. 6	53, 125
May-----	64	-----	14. 44	-----	-----	57, 624
June-----	79	<sup>1</sup> 5	18. 65	1. 18	6. 3	55, 049
July-----	83	<sup>1</sup> 6	10. 73	. 78	7. 2	80, 375
August-----	81	<sup>1</sup> 3	11. 47	. 42	3. 7	91, 772
September-----	95	<sup>1</sup> 5	10. 66	. 56	5. 3	115, 864
October-----	93	4	7. 79	. 33	4. 3	124, 159
November-----	67	3	5. 58	. 25	4. 5	156, 158
December-----	119	13	6. 74	. 74	10. 9	183, 549
Total-----	967	51	9. 96	0. 53	5. 27	68, 228

<sup>1</sup> Reported as "typhus-malaria" deaths.

Source: Essential Technical Medical Data, Southwest Pacific Area, 5 Oct. 1944 (corrected).

Earlier in the year, a flight surgeon had called attention to the lighter incidence among Air Force troops:

Certain correlations have become evident between the military function of troops and their physical condition. The incidence of scrub typhus (tsutsugamushi fever) has been almost negligible among Air Force troops whereas the incidence is considerable among Ground Forces of both the American and Australian Forces.<sup>17</sup>

However, after establishment of Sixth Air Force headquarters and supporting units on Owi Island, there was a sharp increase in incidence in the AAF (Army Air Forces) personnel epidemic. By 10 August 1944, when the epidemic was well underway and the strengths of the Air and Ground Forces were approximately equal on the base, there were 288 cases in the Air Forces and 259 cases in the Ground Forces on Owi Island, and an additional 205 in

<sup>17</sup> Quarterly Report, Headquarters, Fifth Air Force Service Command, dated 10 Jan. 1944.

the Ground Forces on Biak.<sup>18</sup> An account of the epidemic in the Air Forces in Owi-Biak states:<sup>19</sup>

During the week ending 5 August, the epidemic had spread until there was a weekly rate of 750 cases per 1,000 per year. During the week ending 26 August, the weekly rate dropped to 114 cases per 1,000 per year. From 26 August to 11 October, there was an average of 2.3 per day, dwindling to 3 cases in the last 8 days of the period. The latter was the result of negligence in abiding by existing regulations on the prevention of scrub typhus. There has been a total of 716 cases with 3 deaths out of an average strength of approximately 15,000 \* \* \*. Febrile period usually lasted about 2 weeks. Of milder cases, 58 were returned directly to duty; of this number, 18, or 30 percent, had to be rehospitalized because of severe asthenia and symptomatic tachycardia.

In December 1944, there were in the two general hospitals on Biak 32 such readmissions—diagnosis asthenia and neurasthenia—4 of whom were readmitted for the third time including their initial attacks of scrub typhus in August. The total number of primary cases by this time, according to this author's personal observations on 2 December 1944, had reached 1,469 for the two islands, with 7 deaths and a possible eighth in an evacuee, giving the remarkably low case fatality rate of 0.05 percent. On the basis of a conservative estimate of an average loss of 60 to 70 man-days per primary patient,<sup>20</sup> the epidemic on the Biak base represented a potential loss to the Army of 90,000 man-days, or including the Sansapor epidemic, 150,000 man-days potentially chargeable to these two disasters.<sup>21</sup> Epidemiologically, therefore, such low mortality rates and variations in virulence are deceptive in evaluating the military cost chargeable to scrub typhus.

The cost in the military sense is even more strikingly illustrated by experience in the Sansapor epidemic. Within the first 20 days of landing, 403 men were hospitalized in the 1st Infantry Regiment alone. Among these were the regimental commander, executive officer, and 10 other staff officers, 5 company commanders, and 13 other officers.<sup>22</sup> Quoting from another account:<sup>23</sup>

In contrast to "E" [Sansapor], where there were 135 cases with onsets by D+13, only 4 of the cases from the earliest units arriving at "D" [Owi Island] had onsets by that equivalent time after arrival, and the epidemic built up much more slowly at "D". It is not known what the percentage of infection in the respective local mite populations was, but study of the case distribution and questioning of patients suggested that the relatively longer incubation periods at "D" were in part also a reflection of a lower level of virulence.

<sup>18</sup> Personal observations of the author through data supplied by 92d Evacuation Hospital on Owi Island and the other sources, August 1944.

<sup>19</sup> Summers, D. H.: An Outbreak of Scrub Typhus Among Air Force Troops in the Southwest Pacific Area. *Air Surgeon's Bull.* 211: 371-373, November 1945.

<sup>20</sup> Browning, J. S., Raphael, M., Klein, E. F., and Coblentz, A.: Scrub Typhus. *Am. J. Trop. Med.* 25: 481-492, November 1945.

<sup>21</sup> Kohls, G. M., Armbrust, C. A., Irons, E. N., and Philip, C. B.: Studies on Tsutsugamushi Disease (Scrub Typhus, Mite-borne Typhus) in New Guinea and Adjacent Islands: Further Observations on Epidemiology and Etiology. *Am. J. Hyg.* 41: 374-396, May 1945.

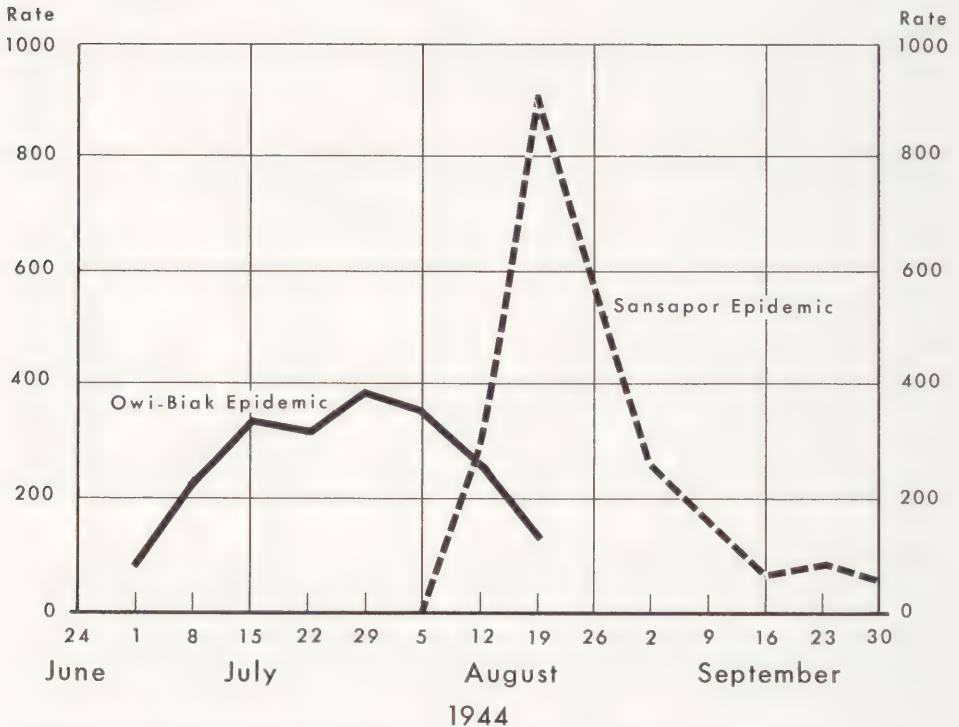
<sup>22</sup> Letter, Lt. Col. Cornelius B. Philip, SnC, United States of America Typhus Commission, to Col. M. C. Pincoffs, MC, Office of the Chief Surgeon, through Chief Surgeon, Sixth U.S. Army, dated 29 Aug. 1944.

<sup>23</sup> See footnote 21.



In 53 days, during the epidemic at Sansapor, a total of 931 cases were hospitalized, with a fatality rate of 3.4 percent. The extraordinary number of nine primary eschars on one patient, and others not infrequently with multiple eschars, indicated that the local mite population must have carried a high rate of infection. Data on admission rates on 1,000 per year basis for the combat periods during the Sansapor and Owi-Biak epidemics are given in chart 18. In view of the strain on hospital facilities and the severity of this infection, the noneffective curve for the Sansapor epidemic is indeed a prodigious one. The peak, which was as an individual episode higher than any yearly rate for all causes in the entire U.S. Army, was reached within 3 weeks of D-day (31 July) and could have been serious if there had been intense enemy opposition.

CHART 18.—*Scrub typhus in U.S. Army Forces in New Guinea, June–September 1944*



[Hospital admission rates expressed as number of cases per annum per 1,000 average strength]

In beachhead or airborne types of combat operations, it was often possible to determine rather exact incubation periods in initial cases, thus aiding local epidemiological observations and determination of foci. The shortest period noticed in Army personnel was a case hospitalized on D+6 in the Sansapor episode, and contracted during bivouac at the mouth of the Wewe River (Mar Village). A U.S. Navy report cites an instance of onset of illness only 4 days

after initial landing.<sup>24</sup> Usually cases appeared in exposed units within 1 to 2 weeks of initial exposure in focal areas as in the 864th Engineer Aviation Battalion and other early units on Owi Islands (see table 46).

On the other hand, at least three episodes<sup>25</sup> occurred in which there was a peculiar delay in appearance of cases for some weeks after units were installed:

The first was in personnel of the 17th Station Hospital at Milne Bay, which moved into and cleared its area in early September; nine cases developed the third and fourth months (November 15 to January 15) long after the presumed maximum exposure had occurred without accountable change in local activity.

In the second instance of delayed occurrence, approximately 200 men were engaged in clearing hospital areas for the adjoining 360th Station and 9th General Hospitals on Goodenough Island during September and October 1943. Both hospitals then moved in late in October resulting in the exposure of some 1,000 persons. Twenty-four cases of scrub typhus appeared in November and December among personnel of the 9th General Hospital. In the patients and personnel of the 360th Station Hospital, the majority of an additional 24 cases occurred in the last half of December, long after maximum exposure would have been expected to occur.

In the third episode, 17 cases developed near Finschhafen in four batteries of an air warning battalion situated in an unusually well cleared area (fig. 15) previously occupied by another battalion which had moved out 6 weeks previously after approximately 3 months' residence without occurrence of any cases. Other unaffected units were in close proximity on all sides. The battery of the subsequent occupants with the most cases had been installed from 88 to 112 days before the onset of illness. Investigation suggested that these 17 cases together with the only 2 that occurred in any adjoining unit were contracted during clearing for and attendance at a newly completed grassy amphitheater in an adjacent ravine (fig. 16). Ironically, the theater was dedicated to the first victim, T. J. Ayres, before it was known that he had probably contracted his infection during initial work on this project.

The last two of these small episodes also involved the highest fatality rates of any individual outbreaks in Army experience—27.5 percent (Goodenough) and 35.3 percent (Finschhafen).

On invitation of the Chief Surgeon, Southwest Pacific Area, a field team was sent by The Surgeon General, through the Board for Investigation and Control of Influenza and Other Epidemic Diseases in the Army and the Director of the United States of America Typhus Commission (hereinafter referred to as USATC), to New Guinea to study the epidemiology, clinical features, and etiology of scrub typhus in the troops. The original five mem-

<sup>24</sup> Logue, J. B.: Scrub Typhus. Report of Epidemic in the Southwest Pacific. U.S. Nav. M. Bull. 43(4): 645-649, October 1944.

<sup>25</sup>(1) See footnotes 13, p. 285; 20, p. 287; and 24. (2) Letter, Lt. Col. C. B. Philip, SnC, United States of America Typhus Commission, 19th Medical Service Detachment (General Laboratory), to Chief Surgeon, U.S. Army Services of Supply, and Director, USATC, 1818 H Street NW., Washington, D.C., 2 Dec. 1944, subject: Investigation of a Small, Localized Epidemic of Scrub Typhus in 478th AAA AW Bn. Base F.



FIGURE 15.—Area occupied by Company C, 478th Antiaircraft Artillery Air Warning Battalion, Finschhafen, British New Guinea.

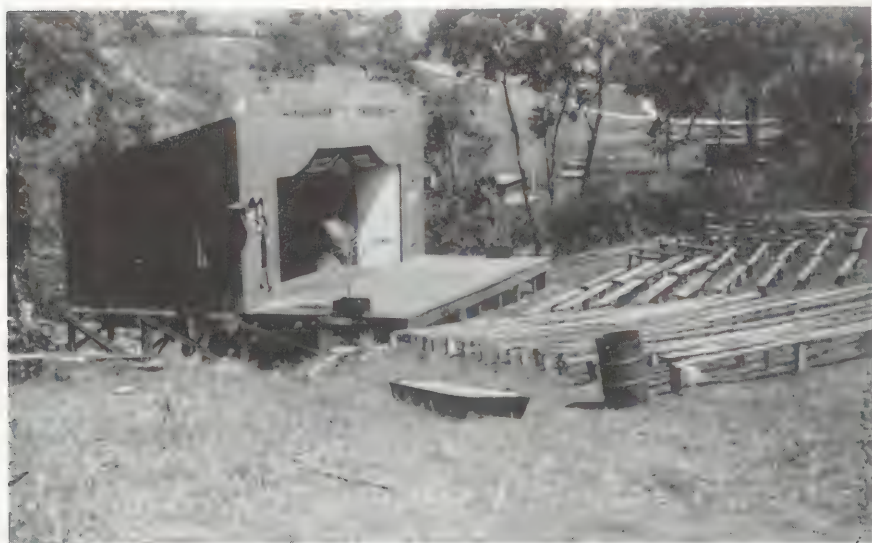


FIGURE 16.—T. J. Ayres theater area. Cases in the 478th Antiaircraft Artillery Air Warning Battalion were traced to this area.



bers of this team set up a laboratory headquarters at the 3d Medical Laboratory, Dobodura, on 19 October 1943.<sup>26</sup> As the disease was increasingly encountered in 1944, one to three new members of this team continued field and laboratory investigations as well as assisting, on invitation, in control work and the indoctrination of troops in antimitic practices. A part of this group then remained with the troops during reoccupation of the Philippines.<sup>27</sup>

### Scrub Typhus in the Philippine Islands

The disease was of only incidental military importance during the operations in the Philippines as compared with the larger New Guinea and Burma episodes. The political importance, however, of finding the first incontrovertible evidence of widespread foci on six islands in the archipelago during military reoccupation in World War II justifies discussion of this experience as a separate major episode in this history of scrub typhus.<sup>28</sup>

Incidence and rates in U.S. forces, from the Army statistical health reports, are separately tabulated for the Philippines in tables 42 and 43, with a total of about 300 reported cases (Naval personnel were also hospitalized on two of the islands).<sup>29</sup> The islands remained a part of the Southwest Pacific Area, though the military authorities in the archipelago were changed in titles respectively from USAFFE (U.S. Army Forces in the Far East) and USASOS (U.S. Army Services of Supply), to AFPAC (U.S. Army Forces in the Pacific) on 3 April 1945, and to AFWESPAC (U.S. Army Forces in the Western Pacific) on 7 June 1945.

The first cases in the Army developed in late 1944 during the campaign on Leyte, but this island remained a very minor focus. These were soon followed by the two largest, though still moderate, outbreaks in Armed Forces on Samar and Mindoro, each of which built up within 5 months to just under 100 military casualties, but only a third of those on Samar were Army cases. Other islands on which small numbers of Army cases originated, mostly during combat operations, were Luzon, Negros, and Mindanao. Those on Luzon were widely scattered, and not more than six occurred in one locality. In spite of report of cases in Japanese troops in unspecified areas of Mindanao, only one proved case was contracted in U.S. Army Forces.<sup>30</sup>

<sup>26</sup> See footnote 3, p. 277.

<sup>27</sup> Philip, C. B., Woodward, T. E., and Sullivan, R. R.: Tsutsugamushi Disease (Scrub or Mite-borne Typhus) in the Philippine Islands During American Re-occupation in 1944-45. *Am. J. Trop. Med.* 26: 229-242, March 1946.

<sup>28</sup> Philip, C. B., and Woodward, T. E.: The Foci of Tsutsugamushi Disease (Scrub Typhus) in the Philippine Islands as Encountered by American Military Forces. *J. Mil. Med. in Pac.* 1(4): 67-69, 3 Dec. 1945.

<sup>29</sup> (1) Memorandum, Maj. R. R. Sullivan, MC, Medical Inspector, Headquarters, Eighth U.S. Army, Office of the Surgeon, for Surgeon, Eighth U.S. Army, 20 Feb. 1945, subject: Scrub Typhus at APO 321. (2) Memorandum, Lt. Col. C. B. Philip, SnC, for the Director, United States of America Typhus Commission, through the Chief Surgeon, U.S. Army Services of Supply, 27 Apr. 1945, subject: Scrub Typhus in Western Visayan Task Force (Mindoro). (3) Memorandum, Lt. Col. C. B. Philip, SnC, for Brig. Gen. S. Bayne-Jones, United States of America Typhus Commission, Washington, D.C., through Chief Surgeon, AFWESPAC, 23 July 1945, subject: Scrub Typhus on Samar.

<sup>30</sup> See footnote 3, p. 277.

In a total of 222 American cases, the occurrence of only 10 deaths or a fatality rate of 4.5 percent revealed no foci of high virulence [data on the remainder of the 300 total cases (table 42) were not available]. Distribution of foci where one or more cases were contracted in the Philippines is shown in map 6.

### The China-Burma-India Episode

The third of the major Army episodes with scrub typhus occurred chiefly along the Stilwell (Ledo) Road in northern Burma during staging and combat operations.<sup>31</sup> The close integration of Chinese troops in these operations emphasized the desirability of reporting their parallel experience with the disease.<sup>32</sup>

While the infection again was found to have localized or "place" occurrence in a given area, it was nevertheless widely distributed in northern Burma. It was encountered in spots along the entire length of the Ledo Road at various times in the operational period of November 1943 through July 1945, as well as at points in the Ledo area of northwestern Assam, in the Fort Hertz district, and in some other outlying areas near Lashio and along the Burma railroad (map 7). During this period, there were five distinct peaks in case occurrence, the first and last concerning chiefly the Chinese, with minor increases in American incidence, while the other three involved U.S. troops in the main. A comparison by months is shown in chart 19 for case rates per 1,000 per year in the Southwest Pacific Area and China-Burma-India theater. The high peak in SWPA in 1944 was due to two major epidemics in New Guinea (p. 288). The five peaks in the CBI curve were a reflection chiefly of combat activities.

Case incidence in the Burma experience was compiled from analysis of hospital records by a member of the USATC Burma team using diagnostic criteria of (1) Weil-Felix OX-K titer of at least 1:200 or a rising titer in spaced serum samples, (2) a fever curve characteristic as to type and duration, and (3) consideration of certain clinical characteristics such as lymphadenopathy, presence of eschar and rash. During the combat period of November 1943 through July 1945,<sup>33</sup> there were in U.S. troops, omitting 55 doubtful cases, 695 cases and 58 deaths from Ledo, Assam, to the Namhkam Trail in Burma (table 45). In Chinese troops of the same combat teams and intermingled areas as seen in map 7, there were 403 cases and 40 deaths from the Ledo to Lashio areas, giving an overall fatality rate of 8.9 percent in the total of 1,098 cases in both groups handled in 3 American general and 3 evacuation hospitals. Again, as in the Philippines, areas of high virulence were not encountered.

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<sup>31</sup> Unless otherwise indicated, the material in this section is based on Van Auken, H. A.: *A History of Preventive Medicine in the U.S. Army Forces of the India-Burma Theater, 1942-45*, pt. III, sec. XV, *Scrub Typhus*, pp. 305-314. [Official record.]

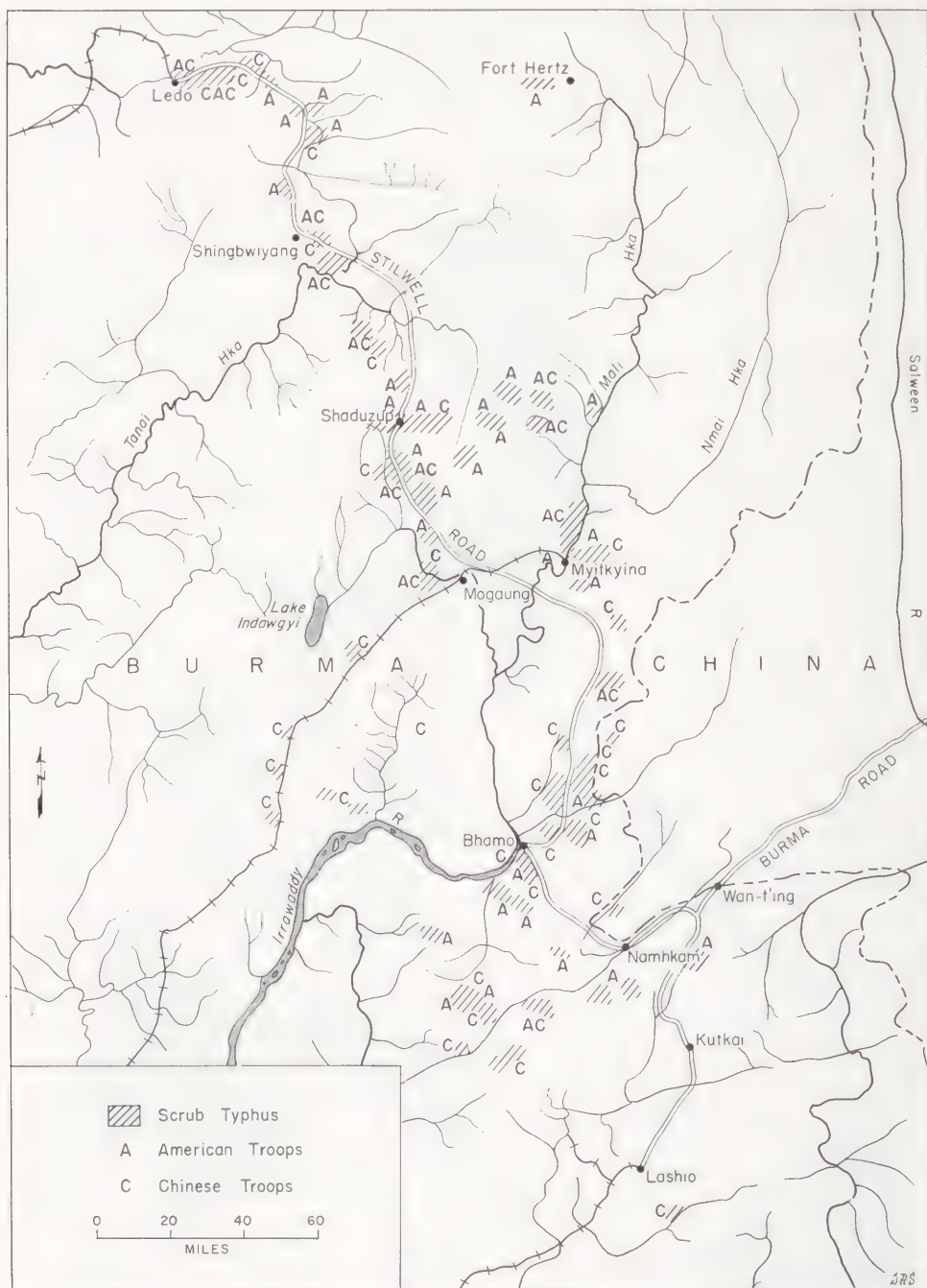
<sup>32</sup> Mackle, T. T., and others: *Observations on Tsutsugamushi Disease (Scrub Typhus) in Assam and Burma. Preliminary Report. Am. J. Hyg. 43: 195-218, May 1946.*

<sup>33</sup> One year earlier than separately reported for Burma-India by the statistical health reports, table 45.



MAP 6.—Location of known foci of scrub typhus encountered by troops on six of the Philippine Islands during American reoccupation in 1944-45. (Phillip, Woodward, and Sullivan, *Am. J. Trop. Med.* 26 : 229-242, March 1946.)

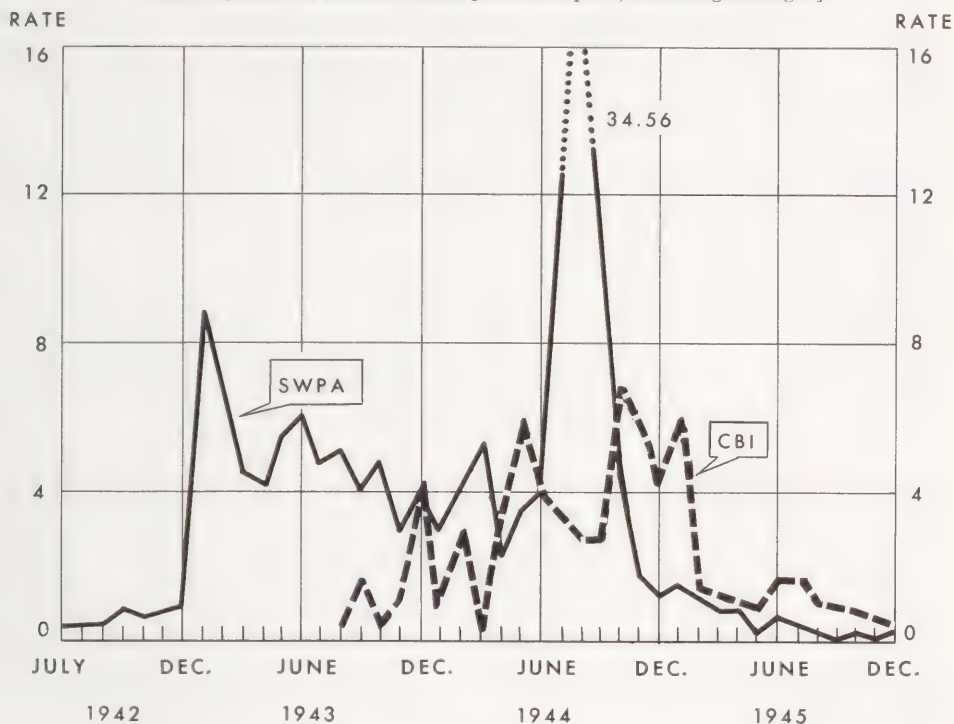




MAP 7.—Areas in which scrub typhus was encountered by staging and combat troops during the campaign in North Burma.

CHART 19.—*Scrub typhus in U.S. Army troops in the Southwest Pacific Area and China-Burma-India theater, July 1942–December 1945*

[Rate expressed as number of cases per annum per 1,000 average strength]



That data on certain of the early Chinese cases are incomplete is due to the destruction of records of approximately 300 cases hospitalized in forward areas by the 25th Field Hospital, Seagrave's Hospital, and a detachment of the 151st Medical Battalion during action. The 44th Field Hospital later also handled forward cases during the siege of Myitkyina.

All but 66 of the American cases and the majority of the Chinese incidences occurred during what were considered as operational or combat activities rather than in Services of Supply operations. Cases occurred in every month of the year, and the plotted curve of incidence in noncombat or service troops shows no correlation with the five peaks of incidence. For example, all but 13 of the 189 American cases comprising the second peak came from the Galahad forces fighting their way toward Myitkyina, the third peak comprised chiefly cases in the 5332d Brigade (Provisional), later called "Mars Task Force" (composed of approximately 6,000 American and 2,000 Chinese troops), on maneuver and field training in a highly endemic area north of Myitkyina, and the fourth peak involved 194 American cases of which 185 were again in the combat battalions of the 5332d Brigade (Provisional) in the Bhamo battle area. The remaining 9 cases thus were scattered among the remainder of the 65,000 U.S. troops in Assam and Burma not in active combat in January

TABLE 45.—*Hospital admissions for and deaths due to scrub typhus in U.S. Army troops, including India-Burma theater, with strength reports for Ledo area and Burma where all cases occurred, November 1943–July 1945*

[Rate expressed as number per annum per 1,000 average strength]

Month and year	Number of cases	Number of deaths	Strength	Rate
<i>1943</i>				
November.....	3	0	( <sup>1</sup> )	( <sup>1</sup> )
December.....	15	1	( <sup>1</sup> )	( <sup>1</sup> )
<i>1944</i>				
January.....	6	0	25, 990	2. 73
February.....	3	0	27, 101	1. 40
March.....	2	0	27, 000	0. 87
April.....	32	2	27, 919	13. 98
May.....	137	25	28, 454	56. 85
June.....	22	0	29, 351	9. 14
July.....	24	0	32, 823	8. 63
August.....	21	1	35, 029	7. 08
September.....	34	1	39, 817	10. 42
October.....	107	3	43, 429	29. 09
November.....	75	2	50, 413	18. 15
December.....	59	2	57, 118	12. 20
<i>1945</i>				
January.....	143	17	65, 243	25. 81
February.....	6	0	69, 571	1. 12
March.....	1	0	71, 522	. 16
April.....	0	0	70, 912	0.
May.....	1	0	67, 394	. 17
June.....	2	2	56, 103	. 43
July.....	2	2	54, 949	. 43
Total.....	695	58		

<sup>1</sup> Data not provided.

Source: Based on survey of United States of America Typhus Commission.

and February of 1945. It was considered therefore that these peaks of incidence were a reflection of field exposure during combat and staging operations rather than a reflection of seasonal factors. This lack of observable seasonal variation was in agreement with observations in the New Guinea and Philippine episodes also, though the limiting exigencies of mobile military operations with consequent fluctuating exposure had to be kept in mind in such attempted evaluation. Though British investigators reported their belief that there was a seasonal relationship to the incidence in their troops in Burma, there was no way to be sure that the same factor of exposure was not also the responsible cause.<sup>34</sup>

<sup>34</sup> Verbal report to author from observers on the Burma team of the United States of America Typhus Commission.



The rate curve (American troops) is seen essentially to follow the incidence curve (chart 20). Accurate Chinese strengths were not available, but it was known that probably more Chinese combat soldiers were engaged in the Burma campaign than were American. Five numbered Chinese divisions were involved.

The first case of so-called "CBI fever" was reported to the Base Surgeon, Advance Section No. 3, Ledo, in December 1943, when the first peak of cases involving mainly Chinese troops in the Ledo and Shingbwiyang areas was already well established. Although scrub typhus was suspected by the medical officers in these advance operations, they were understandably cautious in applying this diagnosis in a new region in the absence of serologic corroboration. So the early cases were reported under the sobriquet of "CBI fever," or simply as F.U.O. (fever of undetermined origin). The early picture also probably was complicated by occurrence of some louseborne typhus in Chinese troops being flown in from China as "delousing procedures were routine and necessary—and louseborne cases in the Chinese ran continuously through the campaign."

The fifth peak in June and July 1945 was more or less a repetition of the first in December 1943, since it again involved mainly Chinese troops staging in many of these same endemic areas, the so-called Namchik encampment area and the 12- to 14-mile marks on the Ledo Road. Figure 17 shows an air-view of the 12-mile encampment focus; an arrow points to the swimming area (shown in fig. 18), on whose grassy banks cases from the two encampments were presumably infected. Recognition that infected mites persist in a developed area for longer than a year was emphasized as a result of this experience.

With the advent of the second peak, it became evident that special attention to preventive measures was necessary. On 31 July 1944, the theater surgeon sent a radio message to Field Headquarters, USATC, in Cairo, Egypt, for any assistance they could provide. The Director, USATC, Washington, then assigned a field party to the theater, the first contingent of which arrived on 22 October 1944. The chronology of their activities has been documented. In that report, graphs are presented comparing data of case occurrence from the special USATC report and from statistical health reports. Discrepancies in totals and time distribution are due to elimination of some doubtful cases and plotting by actual onset in the former, among other differences in handling of the data.

Before the arrival of this special team, investigative work had been initiated through the Office of the Theater Surgeon, and certain basic studies were being carried on at the 25th Field Hospital.<sup>35</sup> One officer and two enlisted men received Bronze Star awards for these studies. The USATC group reached an eventual strength of 14 officers and 36 enlisted men on or attached to the team, which functioned chiefly in investigations of epidemiology and etiology of the disease as discussed later. Among these personnel, 14 were

<sup>35</sup> Annual Report, Theater Surgeon, Headquarters, U.S. Army Forces in China-Burma-India, 1943.

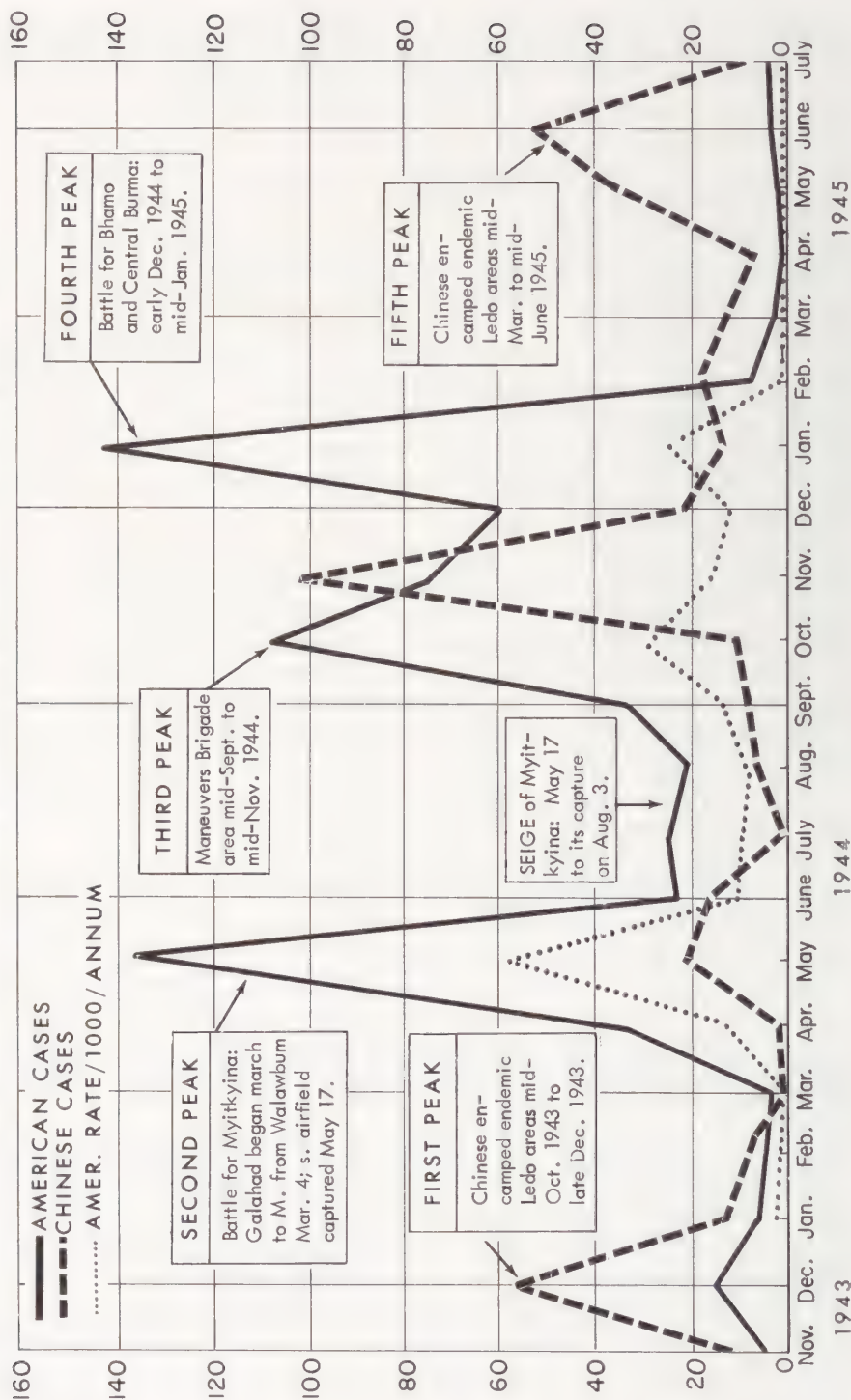
CHART 20.—*Scrub typhus in U.S. Army and Chinese troops in India-Burma theater, November 1943–July 1944*



FIGURE 17.—Airview of “mile-12” focus of scrub typhus on the Ledo Road. Arrow indicates bathing site used by American and Chinese troops. The characteristic Burma rain forest is broken only by occupied or developed areas, or by secondary vegetational growth in abandoned bivouac sites (across the road) previously occupied during the 1943 peak of cases. Natural, open, grassy fields were not encountered until the approaches to Myitkyina.

awarded the USATC medal for meritorious contributions to the study of typhus during the Burma campaign.

Because of the probability that at least some of the listed admissions of reported scrub typhus in China (table 42) had been infected during staging in Burma and flown over during their incubation periods, a clear picture of the actual focal conditions in China is not yet possible. As late as May 1945, a Joint Intelligence Collection Agency report of typhus in civilians states: “Some of the cases occurring in Kweichow and Yünnan in a few respects resemble scrub typhus (OX-K miteborne type), but the presence or absence of this type of typhus fever in China has not yet been fully determined.”<sup>36</sup>

<sup>36</sup> Report, Joint Intelligence Collection Agency, JICA/China, SN R-399-CH-45, Kunming, China, 30 May 1945, subject: China: Typhus Fever in China During Recent Years.





FIGURE 18.—Bathing site on Tirap River indicated by arrow in airview (fig. 17). Exposure to mites on grassy banks is illustrated here.

However, in late 1943, there is record of an American soldier hospitalized in the 100th Station Hospital, Delhi, India, 3 days after onset of symptoms and 6 days after being flown over from K'un-ming where his actual exposure must have taken place. He later presented positive serologic evidence "antigenically similar to the 'Karp' strain from New Guinea."<sup>37</sup> In regard to focal areas in the Chinese area of operations, one other reference, dated 2 May 1945, has been located: "Since 1940, the National Health Administration has knowledge of only five authenticated cases. Four of these were encountered in Kweiyang and one in K'un-ming."<sup>38</sup>

Of the total 56 typhus cases listed from China in statistical health reports between June and November 1945, 18 were specifically reported as scrub typhus. Data on the actual sources of infection, however, still remain in doubt, and the authenticity of any cases in U.S. troops originating in China was seriously questioned by the medical consultant of the China theater Surgeon's Office.

<sup>37</sup> Memorandum, Norman H. Topping, U.S. Public Health Service, to Director, United States of America Typhus Commission, 11 Dec. 1943, subject: Report on Sera From Cases of "Kunming-Fever."

<sup>38</sup> Memorandum, Col. Thomas T. Mackie, MC, Executive Officer, Field Headquarters, USATC, Burma, for Director, USATC, 2 May 1945, subject: Report of China Trip.

who believed the typhus reports from that area to concern chiefly endemic (murine) typhus fever.

### SCRUB ITCH CAUSED BY TROMBICULID MITES

"Scrub itch, or chigger bites" constitute the only other affliction caused by trombiculid mites to which troops were exposed in the areas under discussion, so far as is known.<sup>39</sup> In some areas of New Guinea such as the Buna-Dobodura, Finschhafen, and Sansapor localities, severe reactions due to heavy chigger infestations were often suffered during jungle combat or exercise.<sup>40</sup>

In this case, the reactions were of two types: those due to direct irritation of the bites and those which became secondarily infected because of subsequent scratching and abrasions. Figures are not available on the number of troops reporting to sick call or confined to quarters from this cause, but many cases are known to have occurred on the three bases at the localities cited.<sup>41</sup> In SPA, scrub itch was encountered on Stirling in the Treasury Islands, and in the Munda campaign on New Georgia.<sup>42</sup>

The species of responsible mites varied in different areas. In northern Queensland, where a few American troops were bothered, the species concerned was *Trombicula* "*minor*" (*bulolensis*)<sup>43</sup> while that and two others, namely, *Schöngastia blestowei* and *Schöngastia pusilla* (fig. 19), were responsible in New Guinea depending on the locality.<sup>44</sup> An undescribed species of *Trombicula* was the offender on New Georgia. None of these species was a known vector of scrub typhus, though not entirely free of suspicion (see p. 313). Unlike scrub typhus, in which the victim was seldom aware of the bite which caused the infection until the eschar developed during the incubation period of several days when the responsible mite had disappeared, the irritation set up by even a few scrub-itch-producing bites developed within 24 hours around the attached chiggers and often persisted for nearly a week in uncomplicated cases.<sup>45</sup>

It was remarkable that no reports of scrub itch were forthcoming in troops during the campaigns in the Philippines and North Burma.

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<sup>39</sup> Scabic mites, which produce the dermatologic condition known as scabies, spend their entire life as obligatory parasites on their host and are only distantly related to trombiculid mites to which this history is restricted.

<sup>40</sup> (1) See footnotes 3, p. 277; 20, p. 287; and 21, p. 287. (2) Letter, Capt. Carl O. Mohr, SnC, Headquarters, 30th Malaria Survey Unit, Sansapor, to Commanding General, Far East Air Force, 30 Nov. 1944, subject: Monthly Report for November 1944.

<sup>41</sup> Considerable annoyance was also caused to troops on maneuvers in some parts of the southern United States, as well as to those in Trinidad and Panama, according to verbal reports of several observers returning from those areas.

<sup>42</sup> Malaria News Letter No. 10, Headquarters, Malaria and Epidemic Control, South Pacific Area April 1944.

<sup>43</sup> McCulloch, R. N.: Notes on the Habits and Distribution of Trombiculid Mites in Queensland and New Guinea. M. J. Australia 2: 543-545, 18 Nov. 1944.

<sup>44</sup> See footnotes 3, p. 277; and 21, p. 287.

<sup>45</sup> Personal observations during field studies of the author and colleagues.



FIGURE 19.—*Schöngastia pusilla*, one of the chiggers causing scrub itch in troops.

## THE ETIOLOGY, EPIDEMIOLOGY, AND ECOLOGY OF SCRUB TYPHUS

Numerous field and laboratory studies <sup>46</sup> have been brought to bear on the adequate identification of the disease as encountered in various areas with infection caused by *Rickettsia tsutsugamushi*, the agent of Japanese tsutsugamushi disease. Evidence accumulated (as documented in Army contributions) has consisted of clinical and pathological data, serological studies using both the Weil-Felix (OX-K) reaction and specific complement fixation,<sup>47</sup> recovery of strains of rickettsiae from human, rodent, and mite sources and their comparative studies in laboratory animals, and identification of the mite vectors. Laboratory studies in the different theaters were carried on usually

<sup>46</sup>(1) See footnotes 2, p. 275; 3, p. 277; 16, p. 285; 21, p. 287; 32, p. 292; 35, p. 297. (2) Settle, E. B., Pinkerton, H., and Corbett, A. J.: A Pathologic Study of Tsutsugamushi Disease (Scrub Typhus) With Notes on Clinicopathologic Correlation. *J. Lab. & Clin. Med.* 30: 639-661, August 1945. (3) Irons, E. N., and Armbrust, C. A., Jr.: Relation of the Weil-Felix Reaction to the Clinical Course of Tsutsugamushi Disease. *Bull. U.S. Army M. Dept.* 5: 85-94, January 1946. (4) Bell, E. J., Bennett, B. L., and Whitman, L.: Antigenic Differences Between Strains of Scrub Typhus as Demonstrated by Cross-Neutralization Tests. *Proc. Soc. Exper. Biol. & Med.* 62: 134-137, June 1946. (5) Philip, C. B., and Kohls, G. M.: Studies on Tsutsugamushi Disease (Scrub Typhus, Mite-borne Typhus) in New Guinea and Adjacent Islands; Tsutsugamushi Disease With High Endemicity on a Small South Sea Island. *Am. J. Hyg.* 42: 195-203, September 1945.

<sup>47</sup> Using antigens prepared from New Guinea and Burmese strains of human origin and serums from Japanese recovered patients, serological studies confirmed the identity of the disease in these three widely separated areas.



in hospital laboratories or in Army medical laboratories according to location (fig. 20). Field studies were frequently conducted under trying and difficult conditions, both from a technical standpoint (fig. 21) and in relation to task force perimeters and other combat hazards (fig. 22).



FIGURE 20.—Interior view of United States of America Typhus Commission field laboratory at the 3d Medical Laboratory, Dobodura, New Guinea, during acaricides studies.

The ecology of the disease in certain respects followed to a remarkable degree that of another acarineborne rickettsial disease, namely, the Rocky Mountain spotted fever group of rickettsioses. It showed the same peculiar place localization or "spottiness" of distribution in certain areas. Adjoining companies occupying the same kunai grass flat in the Dobodura staging area, and other localities in New Guinea, under the same environmental conditions with relation to the surrounding sharp jungle margins sometimes showed remarkable differences in incidence, or in comparison with adjoining units with similar activities and apparent comparable exposure.

For example, the early fighting of the Western Visayan Task Force on Mindoro was through fields of tall grass in which focal areas of infection were encountered (fig. 23):<sup>48</sup>

<sup>48</sup> See footnote 29(1), p. 291.



FIGURE 21.—Example of “laboratory work” at a U.S. Army field station set up on Bat Island where high endemicity of scrub typhus caused previous military abandonment of the outpost. Mites from native rats are being injected into white mice, which later became infected.

The greatest number of cases, namely, 25 [of 70 total at the time] occurred in the 503d Parachute Infantry, 15 of these in A Company alone. Of these, six occurred in the 3d Platoon of A Company. Questioning of these cases disclosed the interesting fact that five of the six were in the same split squad. The other half of the same squad in which no cases occurred and which operated separately was approximately 200 to 300 yards away at all times during the first 10 days of the operations on Mindoro [that is, the incubation period].

This was also strikingly illustrated at Sansapor where certain platoons of the 1st Infantry Regiment bivouacked in Mar Village were especially heavily hit.

This localization of foci was encountered in all three major episodes and was found in the classic tsutsugamushi areas in Japan as well. It was visualized as possibly related to more restricted foraging and familial movement in a given environment among local rodent populations carrying infected mites than had been supposed was habitual among field rats and allied small animal hosts. Otherwise, there seemed to be no ready explanation for such marked focal restriction.

Different levels of virulence in various foci were apparent as evidenced by differences in fatality rates, discussed in previous sections, another point of



FIGURE 22.—View of distant Biak Islands, Netherlands New Guinea, during bombing of Japanese-held caves in the coralline ridges near which mite surveys were concurrently conducted in connection with the Owi-Biak epidemic of scrub typhus.

resemblance to Rocky Mountain spotted fever. These differences were more apparent when individual outbreaks were considered rather than a consideration of the overall rate for a given base or area command. A report of cases hospitalized in the 161st Station Hospital at Base F (Finschhafen), Southwest Pacific, relates: <sup>49</sup>

There were 6 deaths in the 38 patients who contracted their disease on this Base, and all the deaths occurred in 1 unit having 16 cases over a period of 3 weeks. Hence the mortality [fatality rate] for this particular unit was 37.5 percent, which is the highest mortality thus far reported in this theater and serves to emphasize the marked variability in the virulence of the various outbreaks in the same as well as in different localities in the New Guinea Archipelago. Another index of the virulence of the outbreak in the unit having the 6 deaths is that 5 of the 10 that survived had to be evacuated to general hospitals \* \* \*.

Of interest by way of contrast is an extremely mild case observed by this author at the 161st Station Hospital on 28 November 1944. This patient was from the same battery having the most cases in this small outbreak and was hospitalized with a 2-day fever and later discharged as "F.U.O." with no other symptoms; while on full duty 21 days later, a sample of his serum gave a positive Weil-Felix titer.

In extreme contrast to the high virulence in the classical areas in Japan with reported mortality rate of 35 to 60 percent is the very low rate of 0.5

<sup>49</sup> See footnote 20, p. 287.





FIGURE 23.—Catching rats in a field of young *Saccharum* grass near San Juan, Mindoro, Philippine Islands, through which the 503d Parachute Infantry Regiment fought and were infected with scrub typhus. The height of mature grass is seen in the background.

percent in the extensive Owi-Biak focus. In a few instances in this epidemic, initial symptoms were so mild as to result in discharge of early patients as F.U.O. followed almost immediately by readmission with frank symptoms. This was further supported by recovery from patients of eight strains of the disease agent, four of which “failed entirely to kill groups of mice and, on further study, the other 4 \* \* \* produced milder infections in laboratory animals than strains isolated in other outbreaks.”<sup>50</sup>

There was no evidence in any of the episodes discussed that the disease had a seasonal cycle such as it has in the temperate climate of Japan. On the contrary, cases were contracted in Army personnel in every month of the year in New Guinea, the Philippines, and Burma. Outbreaks resulted from the fortuities of exposure under the exigencies of military operations and the penetration of primitive areas.

<sup>50</sup> Irons, E. N.: Clinical and Laboratory Variation of Virulence in Scrub Typhus. *Am. J. Trop. Med.* 26: 165–174, March 1946.

This was especially clearly demonstrated in the Burma campaign where outbreaks occurred in five major peaks each related to special combat or staging activities and were not seasonally distributed, except as the wet or monsoon season curtailed both movement and exposure.<sup>51</sup> In the Oro Bay-Dobodura base on New Guinea, after the termination of the Buna campaign in January 1943, sporadic cases continued to crop up in the endemic areas for over 2 years as troops completed training, and replacements of new staging troops resulted in the continued exposure during patrols and "jungle exercises" regardless of the time of the year.<sup>52</sup> On the other hand, the extensive Owi-Biak focus ceased within a year to provide new infection after the final elimination of scattered enemy elements in the interior of Biak and adjacent Soepiori Island, and the consequent cessation of exposure to mite-infested areas on combat patrols and details.<sup>53</sup>

Types of focal environments varied as new episodes were encountered, and it became increasingly clear that there was no such thing as a "typical scrub typhus area." Early in the New Guinea campaign, overemphasis was placed on kunai grass because that was the apparent predominant source of infection in Papua and British New Guinea. Then came the Bat Island and Netherlands New Guinea episodes adding neglected coconut plantations, abandoned native village and garden sites, and margins of climax rain forests to the list of typhus loci, followed on Luzon by cases from mountain scrub areas as high as 3,000 feet altitude, and even from within the rain forest itself in northern Burma and possibly Owi Island.

Figures 24 through 30 show grassy areas in northern Australia (scrub margins), New Guinea (kunai), Philippine Islands (*Saccharum* and cogon), and Ledo vicinity, Burma (*Paspalum*), where cases originated. For comparison, focal areas of "yoshi" grass in the classical endemic Prefecture of Yamagata, Japan, are shown in figures 31 and 32. There appeared to be no satisfactory ecological explanation for the kunai flats and ridges with their margins sharply delimited from dense jungle rain forests in New Guinea (fig. 33). The *Saccharum* through which the 503d Parachute Infantry Regiment fought above Mindoro beaches at San Juan was a dense secondary invader in abandoned canefields. In contrast, the cogon grass and ferns on the slopes of Mount Mandalagan in the margins next the timberline, in which the troops of the 160th Infantry Division and 503d Parachute Infantry Regiment dug their perimeter foxholes, was a primary growth with open grassy spurs extending into the timber along the ridges. All seven cases on the island of Negros were contracted here, and none in the 10-mile stretch of fields below to the beach, much of which closely resembled the Mindoro focal areas and through which considerable fighting and consequent exposure also occurred.

<sup>51</sup> See footnote 32, p. 292.

<sup>52</sup> See footnote 45, p. 301.

<sup>53</sup> Personal observation by inquiry at Biak Army hospitals, 5 November 1945, and at the Base H Surgeon's Office.



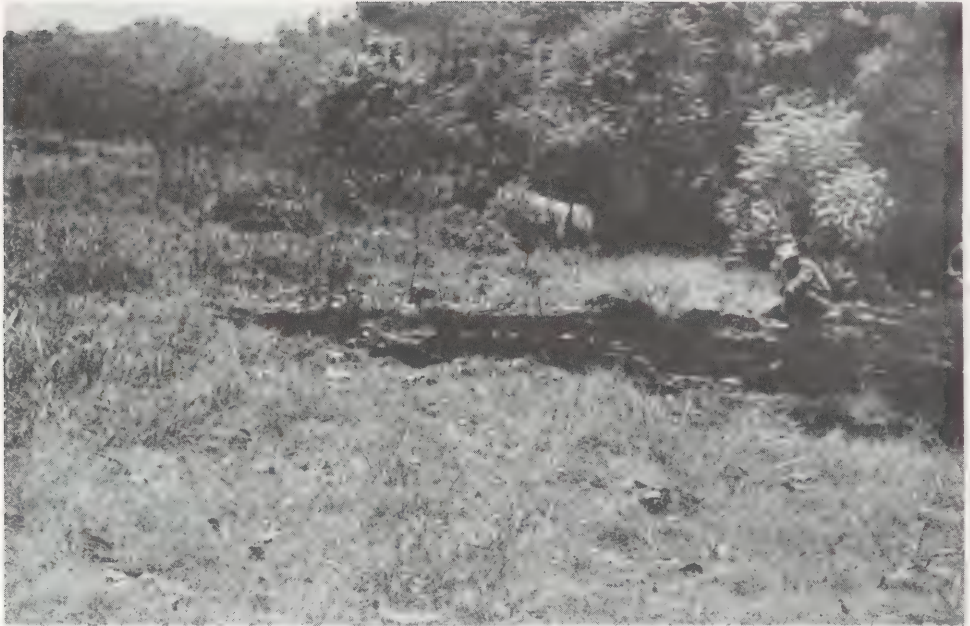


FIGURE 24.—Grassy margin of gum-tree scrub on the Atherton Tableland, northern Queensland, Australia. Typical habitat of *Trombicula minor* where cases of scrub typhus and scrub itch originated during staging exercises.

This variation in environmental types emphasized the unpredictability of potentially infected areas except as surveys revealed the presence of rat- and man-infesting mites as summed up in the following statement:<sup>54</sup>

Within any environment which constitutes a focus of infection lies the fundamental mechanism of natural maintenance, the rat-mite-rat cycle. This conceivably can function under local ecological conditions suitable to the developmental requirements of the mite vectors. Various species of rats are ubiquitous in the regions under discussion. This is stressed because false reliance on a given environmental type as the dangerous one has already misled some recent units that had experienced the disease in previous kunai locations, resulting in a relaxation of vigilance under the new, changed surroundings. Wherever a man is attacked by rat-infesting mites in the Southwest Pacific region, there is the possibility of infection. Not all mites that attack troops, notably scrub-itch mites, are common parasites of rats. The disease is thus focally distributed because of the necessity that both the right mite species and the rickettsial agent be present together to result in human infection.

Cases attributable definitely and solely to tropical or primary rain forest were not encountered in New Guinea,<sup>55</sup> but in Burma this appeared to be the only possible source of infection in a very limited group of troops, and the

<sup>54</sup> See footnote 21, p. 287.

<sup>55</sup> Griffiths, J. T., Jr.: A Scrub Typhus (Tsutsugamushi) Outbreak in Dutch New Guinea. *J. Parasitol.* 31: 341-350, October 1945.





FIGURE 25.—Kunai grass in New Guinea supplying ideal cover for mites and their rat hosts.

vector species of mites was encountered in camps from such an environment.<sup>56</sup> However, some cases in some units during the epidemic on Owi Island are presumed to have become infected during the clearing and location in dense, climax forest, though contact with more open beach areas obviously could not be ruled out.

### THE MITE VECTORS AND ANIMAL RESERVOIRS OF SCRUB TYPHUS

In figure 34 is depicted what was believed to be the diagrammatic scheme of the “rate-mite-rat” cycle of the disease agent as it is maintained in nature,

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<sup>56</sup>(1) Letter, Maj. Dickinson S. Pepper, MC, Headquarters, Base Section 3, Services of Supply, to Surgeon, Headquarters Base Section 3, Services of Supply, 8 Feb. 1944, subject: Report on Investigation of Outbreak of Mite Typhus. (2) See footnote 34, p. 296.



FIGURE 26.—Young kunai grass, secondary growth in abandoned New Guinea campsite of 375th Troop Carrier Group, with sago swamp and rain forest in background. Both vector species, *Trombicula "fletcheri" (akamushi)* and *deliensis*, were taken in boot collections here where an epidemic of scrub typhus occurred.

and the accidental infection of man. Contributions by Army personnel to our fundamental knowledge of vector-reservoir relationships have come from many sources<sup>57</sup> in the Medical Department including observations and collections by malaria survey and control detachments; medical officers of hospitals; medical laboratory, administrative, and combat unit staffs; and scrub typhus investigative teams in both SWPA and CBI sent out from the U.S.A. Typhus Commission.

These studies and observations abundantly amplified information that man is an accidental rather than an essential host in the disease cycle as he is in malaria. They also provided the first conclusive confirmation of trans-

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<sup>57</sup> (1) See footnotes 2, p. 275; 3, p. 277; 10(2), p. 282; 20, p. 287; 21, p. 287; 34, p. 296; 35, p. 297; 40(2), p. 301; and 55, p. 308. (2) Quarterly Report, Headquarters, 30th Malaria Survey Unit, dated 10 Oct. 1944. (3) Memorandum, Lt. Col. C. B. Philip, SnC, for Maj. L. D. Christenson, 403d Malaria Survey Detachment, 24 July 1945, subject: Rodents and Mites, Negros Occidental, P.I. (4) Ahlm, C. E., and Lipshutz, J.: Tsutsugamushi Fever in the Southwest Pacific Theater, J.A.M.A. 124: 1095-1100, 15 Apr. 1944.





FIGURE 27.—Kunai grass in bloom in old camp area near Dobodura, New Guinea.

ovarial transmission (adult to progeny) of *Rickettsia orientalis* in laboratory reared mites.<sup>58</sup>

Two species of mites were demonstrated as actual carriers of infection; namely, *Trombicula akamushi* (fig. 35) (under its synonymic or subspecies name *Trombicula fletcheri*) and *Trombicula deliensis* (fig. 36).<sup>59</sup> The latter had been strongly suspected previously in other areas, but it was first definitely proved in connection with the Bat Island (Admiralty group) epidemic in SWPA (early reports used its synonymic name *Trombicula walchi*).

The two species are very closely related morphologically, and intergrades or variations in certain systematic characters in mites of the *akamushi-deliensis* complex from certain areas in Netherlands New Guinea, the Philippines, Burma, and Japan led to some taxonomic confusion in the absence of adequate rearing techniques. In other foci, identifications of "*fletcheri*" (*akamushi*) and *deliensis* were readily made without these confusing variants being present. Identifications of various Army collections in the main were made by

<sup>58</sup> Davis, G. E., Austrian, R. C., and Bell, E. J.: Observations on Tsutsugamushi Disease (Scrub Typhus) in Assam and Burma; The Recovery of Strains of *Rickettsia orientalis*. Am. J. Hyg. 46: 268-286, September 1947. See especially pp. 281-282.

<sup>59</sup> See footnotes 3, p. 277; 21, p. 282; 32, p. 292; and 46(5), p. 302.





FIGURE 28.—Rat burrows at base of *Saccharum* grass in abandoned cane-fields, Mindoro, Philippine Islands. Ground cover for mites was sparse and dry, but trapped rats carried large numbers of attached mites.

Mr. H. Womersley, South Australian Museum, Dr. H. E. Ewing of the U.S. National Museum, Lt. H. Wharton (USNR), and the entomologists of the USATC scrub typhus teams. Final clarification of the specific components of this vector complex was considered as not yet possible at the close of hostilities though *akamushi* from the classical endemic areas and mite hosts were made available after occupation of Japan.

During these studies, 5 strains of *Rickettsia tsutsugamushi* were isolated in laboratory mice from naturally infected mites in New Guinea and 53 in Burma.

*Trombicula deliensis* was reported by U.S. Army personnel from northern Queensland, many places in New Guinea, the Philippines, northern Burma,<sup>60</sup> and also in the vicinity of K'un-ming, China. This species alone appeared responsible for the Bat Island and Finschhafen (New Guinea), Mindoro and Samar (Philippine Islands) epidemics and many areas along the the Stilwell (Ledo) Road previously discussed. Outbreaks which could have been caused by either or both *deliensis* and *akamushi* (*fletcheri*) according to local mite

<sup>60</sup> Report, Capt. Henry S. Fuller, MC, Chief, Mite Laboratory, USATC in Burma, to Col. Thomas T. Mackie, MC, Executive Officer, USATC India-Burma Theater, dated 6 Dec. 1945, subject: Contributions From Mite Laboratory, India-Burma Field Party.



FIGURE 29.—Young secondary growth of *Paspalum conjugatum* grass in abandoned campsite, Ledo Road, scrub typhus focus at mile-20.

surveys were those in the Dobodura area, Owi-Biak, and Sansapor (New Guinea), Luzon and Negros (Philippine Islands), and certain northern Burma localities.

Hosts of the vector species as found in various Army studies have included a wide variety of animals, rodents, marsupials, insectivores, birds, and man.

In addition to this proved vector group, certain other species that were found in a few focal areas on both rats and men were placed under suspicion. These included two species of *Trombicula*, *wichmanni* and *acutellaris*. The itch mites, *T. bulolensis* or *Schöngastia* species were on occasions the only species found on careful survey following outbreaks in both American and Australian forces in New Guinea. One report stated:<sup>61</sup>

In the early experience, patients hospitalized for miteborne typhus seldom gave a history or exhibited the lesions of scrub itch on admission. At "E" [Sansapor], however, both conditions not infrequently occurred in the same patient showing that exposure to

<sup>61</sup> See footnote 21, p. 287.





FIGURE 30.—3d Tank Battalion area, Ledo Road, mile-12.4 focus, 4 months after abandonment.



FIGURE 31.—“Yoshi grass” on banks of Mogami River, classical tsutsugamushi disease focus, Yamagata Prefecture, Japan, during occupation of the 11th Airborne Division.





FIGURE 32.—“Susuki grass” (*Miscanthus sinensis*) on island in Agano River, Niigata focus of disease, Japan, showing similarity of rat and mite cover to New Guinea kunai grass.

the itch-producing species had occurred probably during the incubation period. In such cases, careful discrimination may be required to differentiate the true primary eschar. Numerous specimens of *Schöngastia* were taken simultaneously with *Trombicula walchi* Womersley and Heaslip 1943 in a focus of intense infection (“E”) [Sansapor], both in boot-collections and on rats. They therefore come under definite suspicion as potential vectors in that area.

However, in most instances scrub-itch-producing species were believed not to be transmitters in consideration of differences in customary location of the lesions and in local host preferences for hosts other than rats. Probably more than 75 new species in over a dozen genera of mites collected from a wide variety of coldblooded and warmblooded hosts, both birds and animals, have been or are in the process of being described as a result of intensive, though necessarily often rapid, survey work by various Army agencies during field operations in SWPA and CBI.

Data from those epidemics in Army episodes did not reveal any necessity for suspecting transmission by arthropod species other than trombiculid mites, though at various times writers made suggestive reference to the need for considering local species of ticks in connection with scrub typhus infection. Species of ticks were taken in several surveys incidental to mite studies but not under circumstances requiring their serious consideration as vectors. The only place reporting any considerable number of tick bites in areas under



FIGURE 33.—Airview of Embi Lakes focus, Dobodura, New Guinea, showing peculiar kunai grass open areas in rain forest, the margins of which are usually sharp, and without ecological explanation.

present discussion was during the early fighting near San Juan, Mindoro, and was reported to this author by the Surgeon, 310th Bomb Wing. Parasitoid mites of several species were present on rats in all areas surveyed. No known attacks on troops by these mites occurred, and their possible role as vectors between rats in nature was unknown.

No evidence was elicited of any important "animal reservoir" of the disease other than rats in the various episodes studied. Because of certain prewar observations in northern Queensland and in New Guinea, concern was felt in the early days of the New Guinea campaign regarding bandicoots (fig. 37), a common ratlike marsupial, often seen about bivouac areas. However, they were not found to be susceptible during laboratory experiments.<sup>62</sup> On the other hand, strains of infection were recovered from two native-caught *Rattus browni* (fig. 38) near Dobodura, New Guinea, and from eight *Rattus flavipectus yunnanensis* in northern Burma. *Rattus praetor* came under strong suspicion as playing a part in the disease focus encountered at the Cape Toro-

<sup>62</sup> See footnote 21, p. 287.

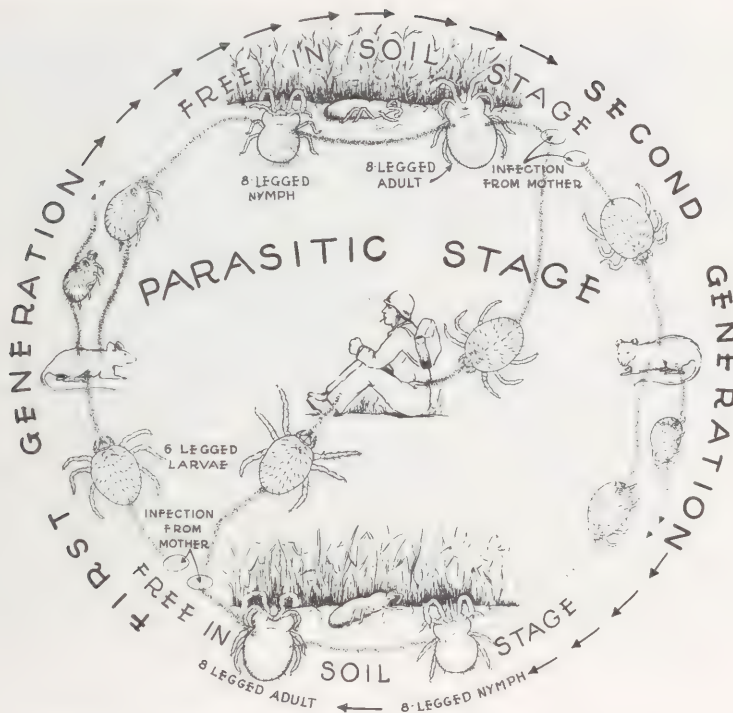


FIGURE 34.—Diagrammatic scheme of theoretical rat-mite-rat cycle of scrub typhus in nature. The "rickettsial stream" is continuous from generation to generation of chigger mites with new lines started from infected rats. Soldiers were accidental intruders in the cycle.

kina beachhead on Bougainville Island.<sup>63</sup> That susceptibility is not confined to Rodentia, however, was shown by recovery of natural infection from four Insectivora, *Tupaia belangeri versurae*, the Assamese tree shrew. The persistence of infection in certain tissues of experimental rats for periods up to at least 98 days is a further fact of fundamental importance adduced in an Army field laboratory.

Many species in several genera of rats, both domestic and native or wild, were taken by various Army agencies in connection with mite surveys, particularly in endemic areas (figs. 39, 40, 41, and 42). Tentative determinations of captured species were sometimes made in the field, but for authentic identifications, specimens, either stuffed or preserved in alcohol, were sent to Mr. E. Troughton of the Australian National Museum,<sup>64</sup> and to Dr. Remington

<sup>63</sup> Johnson, D. H.: The Rat Population of a Newly Established Military Base in the Solomon Islands. U.S. Nav. M. Bull. 46: 1628-1632, October 1946.

<sup>64</sup> Troughton, E.: A Review of Field Investigations Concerning the Mammal Reservoirs of Scrub Typhus in the New Guinea Area. Commonwealth of Australia, Council for Scientific and Industrial Research, Scientific Liaison and Information Bureau, Tropical Scientific Section and Australian Museum, Tropical Scientific Section and Report T.S.S. 2, Melbourne, July 1945.





FIGURE 35.—*Trombicula akamushi* (reported as *T. fletcheri* in early reports), the classical mite vector of tsutsugamushi or scrub typhus.



FIGURE 36.—*Trombicula deliensis* (also called *T. welchi*), the other proved vector of scrub typhus.



FIGURE 37.—One of the important mite hosts in New Guinea, a ratlike marsupial known as the bandicoot, *Echymipara cockerelli* often seen in Army installations at night.



FIGURE 38.—Two species of important mite hosts in New Guinea. The smaller, *Rattus browni*, was found to be naturally infected; it and the larger, *Rattus mordax*, were the commonest carriers of vector species of mites.



FIGURE 39.—An excavated nest of the Japanese vole, *Microtus montebelli*, the important, local animal reservoir of tsutsugamushi disease. No mites were found on these young, though their mother was heavily infested.

Kellogg of the U.S. National Museum.<sup>65</sup> Such specimens have been cataloged and are available for further ecological and systematic studies by specialists in the groups. At least one new species of bandicoot and seven new kinds of rats were taken during the collection of mite hosts in SWPA.

Both domestic and native rats, often carrying mites, quickly invaded new Army installations. Mites on such animals or on camp pets such as dogs were of early concern but later not considered dangerous. These mites habitually attached in the protected folds of the outer ear of their animal hosts. The possibilities of transfer from such hosts to man were considered remote, as were the chances of detached mites continuing development in cleared camp areas or buildings to the parasitic, larval stage of the next generation, a matter of some weeks. However, before it was known that foci of the disease existed in the Philippines, transportation of dogs (potentially mite infested) by plane from New Guinea northward was wisely restricted by the surgeon of the Fifth Air Force.

<sup>65</sup> Kellogg, R.: Two New Philippine Rodents. Proc. Biol. Soc. Wash. 58: 121-124, 20 Sept. 1945.





FIGURE 40.—Japanese farmers digging out voles in mite surveys in Niigata, Japan. Supposedly, “mite-tight” clothing was the only protection from mite bite used by natives.

Domestic rats were also found to move inland with Army operations, particularly during establishment of food dumps and quartermaster supplies. The terrain through which the Army generally operated in SWPA and Burma furnished ideal rat and mite cover in the ground litter, and exposure of troops to mite attacks was inevitable. The volunteer undergrowth in neglected coconut groves and abandoned native village sites was particularly attractive to rats (figs. 43, 44, and 45). The rapidity of reestablishment of secondary growth in an abandoned Army campsite in a focus along the Ledo Road may be seen by comparison of figures 46 and 47.

Although refuse and careless garbage disposal, as well as abandoned Japanese food dump sites, attracted a concentrated rat population, corresponding increases in mites in the relatively short periods of time involved were not observed. The occurrence of free-living, nonparasitic mites about such places sometimes caused confusion to the uninitiated sanitary personnel. Such mistaken identity of harmless forms seen in bulldozer trash heaps along the non-grassy beaches of Owi Island during the early phase of that epidemic caused a needless jurisdictional directive against bathing on the beaches.



FIGURE 41.—New Guinea natives catching rats in pits during mite surveys at Dobodura, New Guinea.

### ANTIMITE MEASURES EMPLOYED DURING CAMPAIGNS

As already mentioned, trombiculid mites were most abundantly encountered by combat forces in primitive rather than in agriculturally developed areas. Consequently, the potentialities of mite attack were universal during the campaigns in New Guinea and northern Burma and more limited in neglected fields in the Philippines and while staging in northern Australia. During the early part of the action in each theater, no special antimites measures were inaugurated other than the usual practices and vigilance exercised in good bivouac and camp sanitation which also contributed to mite reduction. These measures were merely intensified when an outbreak occurred during this early period. The following was reported after the Goodenough Island epidemic:<sup>66</sup>

The first epidemic of scrub typhus occurred from 1 November 1943, and lasted until 15 January 1944. During this period, there were 75 cases with 19 deaths. The areas

<sup>66</sup> Letter, Base Surgeon, Headquarters, Alamo Supply Point 1, Goodenough Island, to Chief Surgeon, Headquarters, U.S. Army Services of Supply, 5 Apr. 1944.



FIGURE 42.—A type of live rattrap employing a buried 50-gallon oil drum with baited sticks for mite surveys of infested rats.

mainly indicted as endemic foci were the hospitalization area and Malauna Bay area. A rigid typhus control program was instituted and turned over to the malarial control and survey units for execution. They were aided by the Engineers, Quartermaster, Angau [Australia, New Guinea Administrative Unit], and unit commanders.

The officers and men of the 12th Malaria Control Unit and three personnel of the 6th Malaria Survey Unit received Bronze Star awards for typhus control work during this epidemic.<sup>67</sup>

The help of such malaria units was increasingly enlisted as the campaign in SWPA progressed to aid in control programs formulated on the basis of studies by the USATC team and other Army agencies.<sup>68</sup> On 14 August 1945, the following directive, Circular No. 42, General Headquarters, AFPAC, was issued during preparations for the final assault on the Japanese homeland:

The responsibilities, training and activities of all agencies concerned with control of malaria will be extended to include preventive measures directed against other epidemic diseases transmitted by insects and other animals.

In the fourth paragraph of a memorandum, dated 14 August 1945, entitled "Training Program in Control of Malaria and Insectborne Diseases," are

<sup>67</sup> General Orders No. 34, Headquarters, Sixth U.S. Army, 2 Mar. 1945.

<sup>68</sup> Letter, Col. Maurice C. Pincoffs, MC, Chief Consultant, Headquarters, U.S. Army Forces in the Far East, Office of the Chief Surgeon, to Lt. Col. Cornelius B. Philip, SnC, United States of America Typhus Commission, 3d Medical Laboratory, 10 June 1944.





FIGURE 43.—Undergrowth in neglected coconut plantations in the Samar, Philippine Islands, focus providing good rat and mite cover.



FIGURE 44.—The area shown in figure 43 after burning with flamethrowers, showing ground surface of porous coralline formations.



FIGURE 45.—Coconut grove ground cover in the area of high endemicity on Bat Island.



FIGURE 46.—Camp area of 1st Motor Transport Regiment, mile-21, Ledo Road focus, immediately after removal of undergrowth.





FIGURE 47.—The area shown in figure 46 from different angle, 4 months after abandonment. Note tent stakes still in place. Secondary growth rapidly reinvades the cleared area.

outlined responsibilities of such personnel for indoctrination of all Army personnel in the military importance of malaria and other insectborne diseases in the following subjects:

Individual protection against mite (chigger) bites.

1. Impregnation of clothes and blankets with Quartermaster Item 51-R-300 (Repellent, insect, clothing treatment).
2. Preparation of bivouac area.
3. Avoidance of mites.

As scrub typhus was encountered in increasing amounts and obviously widespread areas in the interim, special attention became focused on mite control, and it was corroborated that the customary clearing and preparation of campsites was also effective in local mite reduction (fig. 48). This was in part the basis for the 1945 directives cited. Rats trapped subsequent to clearing of military areas became practically mite free, while rats taken in the adjoining jungle margins remained as heavily infested as in previous samples. This was observed in Dobodura, Hollandia, and other areas in New Guinea, and confirmed in close quantitative sampling by the 60th Naval Construction Battalion,<sup>69</sup> 30th Malaria Survey Unit,<sup>70</sup> at Owi and Sansapor, and in Burma<sup>71</sup> during the Ledo Road epidemics.

<sup>69</sup>(1) Fischbach, W. M., and Howell, D. E.: Observations on Tsutsugamushi Disease, U.S. Nav. M. Bull. 45: 423-428, September 1945. (2) Memorandum, 60th Naval Construction Battalion, 23 July 1944, subjects: Impregnation of Clothing Against Scrub Typhus Mites.

<sup>70</sup> See footnote 40(2), p. 301.

<sup>71</sup> See footnote 34, p. 296.





FIGURE 48.—A campsite stripped of all vegetational cover, with tents raised on stilts, was found best to eliminate both rat and mite cover. The officers' living quarters at the 19th Medical General Laboratory, Hollandia, Netherlands New Guinea.

Effective reduction of mites by area clearing was also corroborated by comparative counts of mites crawling on boots of an observer squatting in various types of terrain including campsites and adjoining unaltered grass, brush, or jungle margins (fig. 49).

A method of close observation of mites in the ground litter is shown in figure 50. In 1945, "ground area treatment for control of mites" with insecticide was also proposed but was considered to be impractical for advance military operations.<sup>72</sup> In tests in the mite-infested New Guinea jungle, DDT plus oil was found not to be superior to the oil alone in reduction of mites, and the local mite population was rapidly replaced in the treated area.<sup>73</sup>

On the basis of epidemiological observations of scrub typhus encountered under varying conditions through the New Guinea campaign, the following summary of the conceptions of control was published:<sup>74</sup>

These considerations should serve as a guide for adaptation of practical control measures to the varying requirements of any current military operations. In the absence of a vaccine, these measures come under two headings: Mite reduction and personal protection.

<sup>72</sup> Memorandum, Lt. Col. C. B. Philip, SnC, United States of America Typhus Commission, Southwest Pacific Area, for Brig. Gen. S. Bayne-Jones, Director, USATC, Washington, D.C., through the Chief Surgeon, U.S. Army Services of Supply, 6 May 1945, subject: Ground Area Control Against Mites.

<sup>73</sup> Bushland, R. C.: Insecticides Applied to Forest Litter to Control New Guinea Chiggers. *J. Econ. Ent.* 39: 344-347, June 1946. [*Trop. Dis. Bull.* 43: 1196, December 1946 (abstract).]

<sup>74</sup> See footnote 21, p. 287.



FIGURE 49.—Method of "boot collection" for area sampling of mites, used to supplement surveys for mite vectors by rattrapping.

It is not the province of this report to discuss these at length as we have observed them in the field. Briefly, mite reduction is the most practical and enduring measure where installations are relatively static, and consists of alteration of the environment to produce conditions unfavorable to moisture-sensitive mites in the soil surface. Clearing, burning, sanding and the like take time and machinery when available, more so in wooded areas than in open terrain. During the initial stages, therefore, while the grounds are being exposed and dried out, or with troops deploying in virgin environments, it is necessary to resort to protection of personnel.

Madden, Linquist, and Knipling reported initial studies on the use of insect repellents for protection from North American chiggers. Using modifications and a strict antimite fluid, Maj. R. N. McCulloch developed a program of hand applied fluid in the Australian forces which has been followed in the field. A method of antimite clothing impregnation, using 5 percent emulsion of dimethyl phthalate in 2 percent soap solution, also has been developed by Capt. R. C. Bushland of the United States of American Typhus Commission. Both of these methods have been under rigid study using thousands of mites [fig. 51] and have been shown to be effective in reducing the incidence of scrub typhus. Both methods require strict supervision in the average units as a command function, especially during operations, but the "human equation" makes hand application less reliable in our limited experience with this method. Systematic indoctrination has made it a successful practice among Australian troops, however \* \* \*. The most





FIGURE 50.—Method of close observance of activities of mites on grass stems.

difficult to protect in practice are the foot soldiers on extended patrol in the hills or jungles where every ounce of weight carried is critical.

Unit area clearing was accomplished by various methods and at varying speeds according to availability of manpower and equipment, and with acceleration when local emergencies demanded (figs. 52 and 53). Under the pressure of early logistic demands in a given beachhead or jungle operation, equipment, such as bulldozers, graders, and trucks, was primarily needed in time-limited preparation for combat development of airfields, docks, and roads, and for establishment of perimeters. Similarly, often in spite of known presence of a focus of scrub typhus, even manpower for handclearing of unit campsites was available from pressing combat or operational duties only in the early morning and late evening. Under these circumstances, there was an understandable continuation of new cases in units which did not have the supplemental protection of repellent-treated clothing.

On Owi Island, the pressure to meet the logistic deadline for completion of operating airstrips and docks probably resulted in such continuation of case incidence in the 864th Engineer Aviation Battalion and other local units because of unavoidable delays in complete clearing of their respective unit areas and delay of arrival of emergency supplies of repellent for clothing treatment (table 46). Figures 52 and 53 also illustrate the dense vegetation covering this island that impeded units who had to do clearing by hand only.





FIGURE 51.—Jungle laboratory for natural testing of clothing treated with different miticides during United States of America Typhus Commission studies at Dobodura.

TABLE 46.—*Incidence of cases by onset in certain U.S. Army units during scrub typhus epidemic on Owi Island, New Guinea, July-August 1944, by week*

Units	Arrival date	Initial strength	Cases during weeks ending on—								
			1 July	8 July	15 July	22 July	29 July	5 Aug.	12 Aug.	19 Aug.	26 Aug.
864th Engineer Aviation Battalion	13 June	766	5	17	19	4	6	3	5	4	-----
307th Airdrome Squadron	17 June	259	1	5	4	4	2	1	1	-----	-----
308th Bomb Wing Headquarters Detachment	20 June	266	1	5	11	15	4	1	-----	-----	-----
929th Signal Battalion	21 June	168	1	9	10	16	5	2	2	-----	-----
63d Bomb Squadron	6 July	210	-----	-----	2	5	26	36	12	4	-----
64th Bomb Squadron	13 July	(1)	-----	-----	-----	3	28	37	16	2	3

<sup>1</sup> Data not provided.



FIGURE 52.—Clearing virgin jungle with a heavy Caterpillar tractor, during the epidemic on Owi Island.

Due to an initial shortage of cots, units of the 1st Infantry Regiment were still sleeping on the ground at native-abandoned Mar Village (Sansapor epidemic) on D+13, by which time 135 cases were already hospitalized. In spite of the institution of vigorous clearing and burning (fig. 54), cases continued to pour into local hospitals partly due to lag in onset of illness of men already infected. The fact that cases already incubating the disease continued to occur for at least 2 weeks in a given epidemic, even if theoretically every subsequent mitebite could be prevented, was often difficult to impress on unit commanders busy with various other combat responsibilities.

In the later studies in New Guinea and Burma, it became evident that a potentially dangerous area could be rather quickly determined if either of the vector species of mites were found in the ears of locally trapped rats. In the Burma observations, a correlation was shown between a high percentage of indigenous *T. deliensis* in local mite surveys and so-called "hyperendemic" foci of the disease, as corroborated by recovery of strains of disease from local mites by injection of laboratory animals.

Because such survey methods for predetermination of foci were hardly practical for advance military operations in these primitive areas and since all such areas were potentially mite infested, the procedure adopted as most practical for protection of troops in later operations in 1945 in the Philippines and Burma was the wearing of repellent-treated clothing at least during initial



FIGURE 53.—Campsites stripped from virgin rain forest on Owi Island with bulldozer trash-row between units. Cases in this unit probably were contracted from this environment.

establishment or during periods of exposure in jungle exercises, patrol work, and the like.<sup>75</sup>

Acaricides (crudely termed “miticides”) were first screened or tested against North American chiggers in Florida at the Orlando Laboratory of the U.S. Department of Agriculture in cooperation with the OSRD (Office of Scientific Research and Development), and the Surgeon General’s Office of the War Department.

A subcommittee of the OSRD Insect Control Committee with representatives of these and other agencies held their first meeting on 5 April 1945 to discuss problems of scrub typhus control, at which time the most promising of the acaricides were considered and further plans for their checking in SWPA were discussed. This resulted in the eventual establishment by War Department Memorandum No. 40-205-1 dated 20 September 1946, of the Army Committee for Insect and Rodent Control.

Combat and staging activities provided a large proportion of the cases in both theaters under conditions in which the only defense in the absence of a protective vaccine was the wearing of uniforms protected against mite attacks

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<sup>75</sup>(1) See footnotes 68, p. 323; and 69(3), p. 326. (2) Memorandum, Capt. R. C. Bushland, SnC, for Brig. Gen. S. Bayne-Jones, 16 Nov. 1944, subject: Effect of Clothing Treatment on Incidence of Scrub Typhus at Sansapor.





FIGURE 54.—Mite control during the Sansapor epidemic, by burning and clearing in a highly endemic area (Mar Village) used for bivouac by the 1st Infantry Regiment.

by these acaricidal repellents applied either by hand or as an emulsified dip. Hand application was used in U.S. Forces chiefly as an emergency measure or to fortify protection under certain critical conditions, such as during investigations on hyperendemic Bat Island. Following initial studies which determined the efficacy of impregnated clothing for protection from mite attack at Dobodura<sup>76</sup> by the USATC, the first large-scale field use of this method of protection was by the 31st and 37th Infantry Divisions staging in the Oro Bay area in the spring and summer of 1944.<sup>77</sup> The feasibility of wearing such treated clothing under jungle conditions was demonstrated. It also answered the need for protection of personnel exposed in foxholes and temporary air raid shelters and fighting through grass. It was therefore possible to recommend this as a supplemental measure of control by mid-July 1944, when the Owi-Biak epidemic started:<sup>78</sup>

Two members of the Typhus Commission volunteered and were sent to the area to assist and observe the effects of impregnation of clothing with soap suspension of dimethyl phthalate. They arrived on 18 July (D+20) and were helpful in encouraging and demonstrating the method which had been recommended. The process was adopted with enthusiasm by commanders of air and ground forces since the outbreak was large enough to cause serious depletion of troop strength. Evaluation of its effect is not possible in this instance since methods of rodent and mite control were instituted simultaneously.

<sup>76</sup> The Prevention of Scrub Typhus. Bull. U.S. Army M. Dept. 83: 1-2, December 1944.

<sup>77</sup> (1) See footnote 45, p. 301. (2) Training Circular No. 18, Headquarters, 31st Infantry Division, Office of the Division Commander, dated 14 June 1944.

<sup>78</sup> See footnote 14, p. 285.



FIGURE 55.—Indoctrination by Lt. Col. C. B. Philip, SnC, of troops of 308th Bombardment Wing in mite and disease control prior to demonstration of clothing impregnation with acaricide, during the Owi Island epidemic.

During this epidemic, demonstrations were made before key personnel of every unit as well as to many units in other staging areas in New Guinea. After initial indoctrination of mite and scrub typhus control practices (fig. 55), soap emulsions of dimethyl phthalate were prepared and formations were instructed in clothing impregnation (figs. 56, 57, and 58). Thereafter most units kept constant supplies of emulsion available (fig. 59).

The experience gained up to this time was incorporated in Technical Memorandum No. 9, Headquarters, USAFFE, dated 6 August 1944, subject: Control of Scrub Typhus.

Problems of supply prevented the most effective universal practice of this method, but in reports of the Sansapor and Bougainville epidemics, protection was apparently demonstrated for units wearing impregnated clothing as compared with higher incidence of disease of unprotected units under conditions of similar or identical exposure.<sup>79</sup> The intensification of antimite measures in a given beachhead as an epidemic progressed is illustrated in successive directives (11, 19, and 29 August 1944) of Headquarters, 13th Air Task Force, at Sansapor. Emergency repellent for clothing treatment was flown in for their use, and this author observed that the attack rate among their personnel re-

<sup>79</sup> Protection Against Scrub Typhus. Bull. U.S. Army M. Dept. 5: 2-3, January 1946.



FIGURE 56.—Dimethyl phthalate being removed from bottles. Before bulk dimethyl phthalate became available, the acaricide had to be removed by this tedious procedure before emulsification.

remained well below that of neighboring ground forces of the 6th Infantry Division.

Bulk dimethyl phthalate in gallon containers became available in the Southwest Pacific Area, in the summer of 1944, and simplified impregnation routines by units. The use of Quartermaster mobile laundry units (fig. 60) for bulk clothing treatment on three New Guinea bases was instituted shortly before the initiation of the Philippine campaign.<sup>80</sup> Personnel and equipment of the Chemical Warfare Service<sup>81</sup> aided both in development of practical procedures and in emergency bulk antimitic treatment of uniforms.<sup>82</sup>

Most of the task force operations during reoccupation of the Philippine Islands were by troops protected in this way. Evaluation of the protection afforded was difficult, but the low incidence on Leyte and Mindanao was suggested (though also questioned) as having been due to this protection. Bulk repellent with emulsifier added to facilitate field impregnation was recommended in December 1944 but did not arrive in the field in time to be used extensively.

<sup>80</sup> Chemical Warfare Service Monthly Progress Report on Insect and Rodent Control, June 1945, No. 4, p. 32.

<sup>81</sup> (1) Letter, Maj. J. J. Jones, AGO. Asst. AG, Headquarters, U.S. Army Services of Supply, to Commanding General, Far East Air Forces, subject: Chemical Processing Companies. Inclosure No. 1, thereto, subject: Impregnation of Clothing and Blankets with Dimethyl Phthalate Solution as a Protective Measure Against Scrub Typhus. (2) See footnote 22, p. 287.

<sup>82</sup> This has been standard procedure since the Korean War in 1950.





FIGURE 57.—Concentrated dimethyl phthalate soap emulsion being poured into container during demonstration to 92d Evacuation Hospital personnel of anti-mite clothing treatment. Note GI (kitchen) wire egg whip used to emulsify repellent-soap mixture.

In January 1945, with the help of some 200 volunteers (figs. 61 and 62), jungle tests by the USATC near Hollandia proved the superiority of benzyl benzoate and dibutyl phthalate over dimethyl phthalate for both durability and laundry resistance.<sup>83</sup> The former was put into procurement by the Quartermaster, subsequent to its recommendation in March 1945, but the capitulation of Japan circumvented distribution among staging units. Subsequent laboratory and field tests have resulted in improved general purpose impregnants and insecticides on the Department of the Army Quartermaster supply shelf.<sup>84</sup> In December 1944, War Department Technical Bulletin (TB MED) 121 was also published, giving information on impregnation of clothing with insect repellent.

<sup>83</sup>(1) Letter, Col. C. B. Philip, SnC, Executive Officer, United States of America Typhus Commission, 19th Medical Service Detachment, to Chief Surgeon, Headquarters, U.S. Army Services of Supply, through Base Surgeon, Base G, 27 Feb. 1945, subject: Anti-mite Impregnated Clothing Tests, Preliminary Outline. (2) Bushland, R. C.: New Guinea Field Tests of Uniforms Impregnated with Miticides to Develop Laundry-Resistant Clothing Treatment for Preventing Scrub Typhus. *Am. J. Hyg.* 43: 230-247, May 1946.

<sup>84</sup> Department of the Army Table of Allowances No. 10-100-12, 5 Aug. 1949, with change, 31 Mar. 1950.



FIGURE 58.—Formation of 864th Engineer Aviation Battalion personnel on Owi Island for immersing clothing in acaricide emulsion. Stirring with stick in 50-gallon drum keeps emulsion from settling; immersed clothing is wrung out over GI can to save excess solution.

The surgeons of both the Sixth and Eighth U.S. Armies, which were staging in the Philippines, had requested in June and July 1945 that stock impregnation of combat issue clothing be considered, but it was later decided, after consultation of representatives of various agencies concerned, to recommend that woolen clothing not be impregnated for wear between October and June which would include the projected Operation CORONET against Honshu in early December.<sup>85</sup> The Chemical Warfare Service and Quartermaster in Manila had completed plans for request for clothing impregnation if this had been demanded by units going into priority areas in Japan in this final assault.

Clothing impregnation with miticides was never practiced in Burma to the extent that it was in SWPA during military operations.

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<sup>85</sup>(1) Personal observations during consultations with the surgeons of the Sixth and Eighth U.S. Armies on Luzon and Leyte, respectively, June 1945. (2) Memorandum, for The Surgeon General, U.S. Army, through Chief, Preventive Medicine Service, SGO, from Director, United States of America Typhus Commission, 7 Aug. 1945, subject: Impregnation of Woolen Clothing Against Mites.

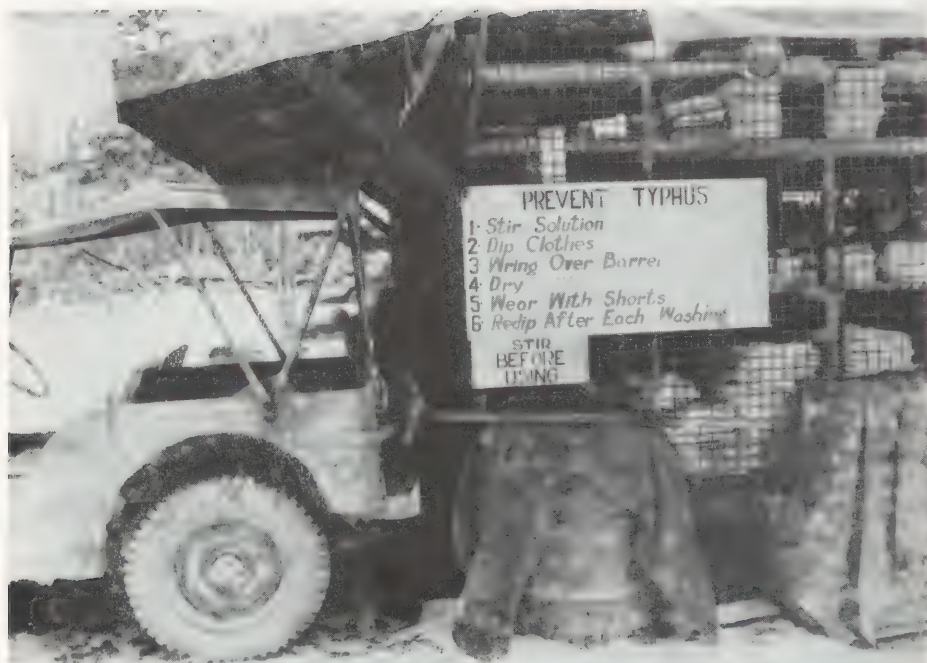


FIGURE 59.—Vats of emulsion. These were kept on hand at all times during Owi epidemic for re-treatment of uniforms, 60th Naval Construction Battalion installation.



FIGURE 60.—Chemical Warfare Service M1 plant converted to mass treatment of uniforms with acaricide, Hollandia, Netherlands New Guinea.





FIGURE 61.—Volunteers from the 20th Replacement Depot, Hollandia, Netherlands New Guinea, wearing uniforms impregnated with different acaricides during United States of America Typhus Commission tests of improved, laundry-resistant emulsions, undergoing 2-hour jungle exposure to heavy chigger infestation.

Prevention and control of scrub typhus during combat and staging in connection with the three major episodes discussed in this history consisted in the main of preparation of campsites to eliminate mites, and of the use of so-called miticides for either hand treatment (fig. 63) or impregnation of uniforms (fig. 58) to protect troops in primitive, uncleared areas.

Certain measures were taken during epidemics which augmented these practices. During the Owi epidemic, all Air Forces personnel were required to mark a yellow "X" on the backs of treated fatigue uniforms to indicate both indoctrination of antimite practices, as well as clothing treatment. Some units also required date of impregnation painted on their uniforms.

Items were prepared for local, daily newssheets of various units to stimulate antimite consciousness among the men.<sup>86</sup> Posters were also prepared to impress the need for caution in regard to the disease (figs. 64 and 65). Directives were issued when needed, restricting certain activities, correcting wearing apparel, and placing dangerous areas "off limits" as indicated by the local emergency.<sup>87</sup>

<sup>86</sup> Newssheets, "The Gag," 60th Naval Construction Company, U.S. Navy [Owi Island], No. 2, vol. IX, and No. 1, vol. X, dated 2 Aug. 1944 and 1 Sept. 1944, respectively.

<sup>87</sup> Memorandum, Headquarters, Sixty-Third Infantry, Nos. 37 and 40, dated 12 Aug. 1944 and 15 Aug. 1944, respectively.



FIGURE 62.—Officers volunteering for same jungle exposure as shown in figure 61.

## SUMMARY

The total number of cases of scrub typhus in U.S. Army Forces in all areas from March 1942 through December 1945 was 6,717 (table 40 gives an amended total of 5,441, based on sample tabulations of individual medical records) as reported by the statistical health reports in the Surgeon General's Office. Presentation of such statistical data necessarily precedes discussion of the epidemiological and focal features of the disease in the Army experience after correction to exclude other known incidence of epidemic (louseborne) and endemic (fleaborne) typhus.

Cases were distributed as follows: Southwest Pacific Area, 5,718; South Pacific Area, 32; and China-Burma-India theater, 967. Omitting from consideration the small number of South Pacific Area cases, the respective hospital admission rates per 1,000 per year were as follows: SWPA, 3.34 and CBI, 2.23.

Epidemiological data pertaining to these are discussed as three major Army episodes geographically: (1) New Guinea and adjacent areas, (2) the Philippine Islands, and (3) the CBI where the bulk of the incidence was in north Burma. Scrub typhus was of only incidental military importance during reoccupation of the Philippine Islands, and there was only negligible incidence in the South Pacific Area, northern Queensland, Australia, and Assam, India.



FIGURE 63.—Contrast of American and Japanese precautionary measures prior to hunt for mite-bearing rodents in Niigata, Japan. Hand-applied dimethyl phthalate is used by Americans; the Japanese puts on a one-piece suit with wrap leggings and canvas (split-toed) shoes.

Documentary confirmation of the origin of reported cases in China is almost totally lacking. One serologically confirmed nonfatal Army case was apparently infected near K'un-ming.

The few cases in U.S. forces in the South Pacific were contracted on Bougainville, New Georgia, and Espiritu Santo. Three proved cases on Espiritu Santo constituted the farthest east the disease has been encountered in military or previous civilian experience.

No cases developed during the noncombat occupation of the endemic areas in northwestern Honshu, Japan, in the fall of 1945 (though a number of cases developed in U.S. troops in a new focus on the slopes of Mount Fuji during staging in 1948).

Two epidemics starting immediately after the landings on the Owi-Biak Islands and at the Sansapor beachhead in Netherlands New Guinea developed into the most serious episodes experienced. In 5 months, 1,469 cases were





FIGURE 64.—Posters developed in the Office of The Surgeon General for field distribution to control scrub typhus.



FIGURE 65.—Poster used in Southwest Pacific Area to combat scrub typhus.

hospitalized during the Owi-Biak epidemic, and at Sansapor, 931 cases in 53 days. The 1st Infantry Regiment of the 6th Division was rendered almost completely noneffective militarily within a month of landing at Sansapor.

Judged by fatality rates, virulence varied in different areas, but the greatest extremes were encountered in local epidemics in New Guinea; namely, 0.5 percent at Owi-Biak to 35.3 percent at Finschhafen. The average fatality rate in the three major episodes covered in this history was between 5 and 10 percent.

A large proportion of cases in all areas was contracted during combat or staging maneuvers in primitive environments. Peaks of incidence were related to such military activities in the American experience rather than to seasonal influences.

No one ecological type was identifiable as a typical scrub typhus focus, and the variation in environments in contributing to the infection of troops as the campaign progressed indicated the impossibility of predicting focal areas ahead of occupation. Foci were encountered in fields of native grass, neglected coconut plantations, abandoned native villages, vine-grass margins of tropical rain forest, and, at least in Burma, even in primary jungle.

U.S. Army agencies contributed fundamental epidemiological information of the disease incidental to the primary medical and preventive functions of the Medical Department:

1. Transmission of the disease through the agency of larval, trombiculid mites or chiggers was abundantly confirmed in the laboratory and circumstantially. No evidence was obtained of other arthropods, such as ticks, acting as vectors.

2. Two vector species of mites were incriminated circumstantially in several foci; namely, *T. deliensis* (synonym *walchi*) and *T. akamushi* (synonym *fletcheri*). Each was confirmed by animal experimentation in U.S. Army field laboratories in New Guinea and in Burma where 5 and 53 strains, respectively, were recovered from naturally infected mites. Hyperendemic areas in Burma were shown to have a correlation between high incidence following exposure and a high percentage of *T. deliensis* in mite samples on indigenous rats.

3. Transovarial (generation to generation) transmission of the disease agent was confirmed in laboratory reared mites in the Burma studies.

4. Strains of infection were also obtained from indigenous species of rats in both New Guinea and Burma, and from Assamese tree shrews.

5. The identity of the strains of disease encountered during the three major episodes with one another and with classical Japanese tsutsugamushi disease was confirmed serologically and by animal experimentation.

Control measures adopted during military operations in the absence of an available protective vaccine were of two sorts: personal protection and mite avoidance, and mite reduction by environmental manipulation or intensive clearing of campsites. Clearing, burning, and camp sanitation were the methods chiefly relied upon early in the campaign to reduce hazards where foci were encountered, but this did not always prevent the continuation of cases. A method of clothing treatment with a 5-percent emulsion of insect repellent, developed by the USATC team in New Guinea, was widely used during 1945 in endemic areas for protection of both combat and staging troops.

The Army experience with scrub typhus was unfortunate in that many thousands of man-days were lost, but it never became strategically critical, although it might have at the Sansapor beachhead if enemy resistance had been heavy. Under the impetus of military pressure, knowledge of the disease and its geographic distribution in the Pacific-Asiatic region was vastly expanded and techniques of protection and control were developed which will be of profound benefit not only in the further postwar development of the endemic areas but also in protection against chigger attacks in other parts of the world.

## ADDENDUM

### Scrub Typhus in the Japanese Forces

A complete chronicle of information on scrub typhus in the Japanese combat forces does not belong in this history, but it is not out of place to call attention to a considerable collection of documents which accumulated in both the Southwest Pacific Area and the



China-Burma-India theater from various sources of interrogation of prisoners, translations of captured medical reports, and intelligence reports. No attempt has been made here to give more than a few examples which will serve to provide some idea of geographic distribution of Japanese cases. More complete Japanese military documentation is given in Hayakawa's postwar report.<sup>88</sup>

The lack of any racial difference in susceptibility to scrub typhus between Chinese Orientals and Caucasians was apparent in the preceding account of the Burma experience.<sup>89</sup> It was learned that the disease also was experienced by the Japanese forces in northern Burma, where it was sometimes referred to as "Burma eruptive fever," or given a place or descriptive name as "Tenta (Burmese for bushy swamp)<sup>90</sup> disease." The infection was sometimes described in medical reports with typhoid-like symptoms, but negative Widal's, sometimes likened clinically to "miteborne typhus fever" with strong OX-K agglutination and other symptomatic similarities. Specific Burma locations mentioned include: Upper Chindwin, vicinities of Mandalay, Sagaing and Amarapura, Wuntho and other villages within 100 miles of Mandalay. Fatality rates were low (one specific figure 7.4 percent), but "numbers of men" passing through the Somra Hills east of Kohima became infected. "Most of the patients contracting the fever died after about 14 days."<sup>91</sup> There is record of a special field study which included injection of laboratory animals and reported recovery of rickettsiae from "Nanking mice" infected with patients' blood.<sup>92</sup> This was undoubtedly one of the strains studied by Hayakawa in Singapore and on which he later based its new name, *Rickettsia orientalis* var. *tropica*.<sup>93</sup>

Captured enemy documents<sup>94</sup> have indicated that hospitalization of tsutsugamushi-like fevers had occurred during Japanese operations both in New Guinea and in the southern Philippines. The laboratory sections of certain of their hospitals and water purification units were probably equipped to do Weil-Felix tests. While their medical reports called attention to the similarity of cases in certain areas to tsutsugamushi or flood fever of Honshu often with positive OX-K serology, they appeared reluctant so to name the disease encountered in southern combat areas. Instead, we find reference to such names as "Hansa Bay" and "Wewak" fevers. It is difficult to believe that when they were driven into the coralline ridges of Biak and bivouacked in Sansapor Village they would have missed encountering the disease, but captured prisoners with medical background were not plentiful for questioning in this regard.

Captured documents indicate that cases were encountered by the Japanese in western New Britain, and a medical report gives data on 65 cases with 2 deaths in their First Field Hospital at Madang. Positive OX-K titers of 800 or more were observed in 22 instances.

While there was only one recorded case in the U.S. forces on Mindanao in the Philippines, an ADVATIS report<sup>95</sup> indicates there were cases among Japanese troops in an

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<sup>88</sup> Hayakawa, K.: A Comparative Study of Japanese and Tropical (Scrub Typhus) Tsutsugamushi Disease (*R. orientalis* var. *tropica*), 13 Feb. 1946. (Obtained on reoccupation of Malaya as military report of Lt. Col. Kiyosi Hayakawa, Medical Corps, Japanese Army, Assistant Director of the Japanese Army Institute for Preventive Medicine, Singapore.)

<sup>89</sup> See footnote 32, p. 292.

<sup>90</sup> See footnote 88.

<sup>91</sup> JICA/CBI/SEA, Report No. 9082, New Delhi, India, 23 Oct. 1944, subject: Tactics and Strategy of the Japanese Army in the Burma Campaign. From November 1943 to September 1944.

<sup>92</sup> Translation Report No. 33, SEA, TIC (South-East Asia, translation and Interrogation Center), 8 Sept. 1944, subject: On the Frequent Occurrence of an Obscure Fever in Northern Burma. Part I. Hayashi Group Medical Data 38, 9 Jan. 1944.

<sup>93</sup> See footnote 88.

<sup>94</sup> (1) See footnote 26, p. 277. (2) Letter, Lt. Col. C. B. Philip, SnC, to Brig. Gen. S. Bayne-Jones, Director, United States of America Typhus Commission, Washington, D.C., 15 Jan. 1945. Inclosure thereto, 13 Jan. 1945, subject: Notes on References to Scrub Typhus in Captured Enemy Documents and Interrogation of Prisoners.

<sup>95</sup> ADVATIS Bulletin No. 64, Advanced Allied Translator and Interpreter Section, Southwest Pacific Area, 14 Dec. 1944. Translation of Medical Intelligence Report (Japanese).

unspecified area on that island. Again, the disease was only likened to tsutsugamushi disease, but not diagnosed as such in spite of positive Weil-Felix reactions and presence of rash and adenopathy.

Subsequent information became available in an extensive report of investigations by Hayakawa,<sup>96</sup> who decided that the tropical disease encountered by the Japanese forces was a variety of the more severe malady in the homeland. Studies and descriptions of mites, reservoir animals, and the ecology of the disease are included in the report. The scattering incidence he reports corroborates the lack of any central collecting agency for data on military cases for, "not a case was reported in Luzon, the Philippines," and their Mindanao episode was unknown to him.

### The Postwar Army Experience and Accomplishments

"Overnight as it were a once severe and often mortal disease, centuries old, much feared by planter and serving soldier alike, had become trivial" was the memorable statement made in the 1951 Jubilee Volume (No. 25) of the Institute for Medical Research Federation of Malaya, Kuala Lumpur. This was a tribute to the dramatic success of the first antibiotic, Chloromycetin (chloramphenicol), shown to be effective in field trials of chemotherapy and prophylaxis against scrub typhus by a cooperating Army team, under leadership of Dr. Joseph E. Smadel, sent to Kuala Lumpur in several contingents beginning in 1948. After demonstration that this drug could be relied upon as a curative,<sup>97</sup> the chemoprophylactic efficacy was investigated by exposure of Anglo-American and native volunteers in hyperendemic locations with the remarkable initial result that 29 of 46 persons became infected in the first test;<sup>98</sup> though the climatic influence on abundance of vector mites was reflected in variable attack rates in the series of exposures, the infection rates in equivalent control and prophylactic groups were essentially the same. The drug, however, suppressed appearance of frank symptoms in the treated groups until several days after cessation of administration of the drug.<sup>99</sup> This and subsequent information gained<sup>100</sup> is of military value but was recognized as less feasible for general civilian use except under unusual circumstances. In treatment, it was found that there was usually prompt favorable response to as little as 4 to 5 gm. in a single, oral dose. Occasional relapses were amenable to the same treatment. The treatment recommended as a result of these studies is an initial 60 mg. per kilogram of body weight followed by 0.25 gm. doses at 3-hour intervals for 24 hours.<sup>101</sup> Weekly dosages of 4 gm. for 4 to 6 weeks were also found to be adequate for chemoprophylactic suppression in volunteers some of whom had proven, concomitant rickettsemia, but only one on the shorter regimen had frank enough symptoms to require hospitalization.<sup>102</sup>

<sup>96</sup> See footnote 88.

<sup>97</sup> Smadel, J. E., Woodward, T. E., Ley, H. L., Jr., Philip, C. B., and Traub, R.: Chloromycetin in the Treatment of Scrub Typhus. *Science* 108: 160-161, 13 Aug. 1948.

<sup>98</sup> Philip, C. B., Traub, R., and Smadel, J. E.: Chloramphenicol (Chloromycetin) in the Chemoprophylaxis of Scrub Typhus (Tsutsugamushi Disease). I. Epidemiological Observations on Hyperendemic Areas of Scrub Typhus in Malaya. *Am. J. Hyg.* 50: 63-74, July 1949.

<sup>99</sup> Smadel, J. E., Traub, R., Ley, H. L., Jr., Philip, C. B., Woodward, T. E., and Lewthwaite R.: Chloramphenicol (Chloromycetin) in the Chemoprophylaxis of Scrub Typhus (Tsutsugamushi Disease). II. Results With Volunteers Exposed in Hyperendemic Areas of Scrub Typhus. *Am. J. Hyg.* 50: 75-91, July 1949.

<sup>100</sup> Smadel, J. E., Traub, R., Frick, L. P., Diercks, F. H., and Bailey, C. A.: Chloramphenicol (Chloromycetin) in the Chemoprophylaxis of Scrub Typhus (Tsutsugamushi Disease). III. Suppression of Overt Disease by Prophylactic Regimens of Four-Week Duration. *Am. J. Hyg.* 51: 216-228, March 1950.

<sup>101</sup> Smadel, J. E., Woodward, T. E., Ley, H. L., Jr., and Lewthwaite, R.: Chloramphenicol (Chloromycetin) in the Treatment of Tsutsugamushi Disease (Scrub Typhus). *J. Clin. Invest.* 28: 1196-1215, September 1949.

<sup>102</sup> See footnote 100.

Subsequent to the earlier of these studies, it was also found both in the laboratory and in the field that Aureomycin (chlortetracycline) and Terramycin (oxytetracycline) are similarly efficacious, though the possibility of "untoward reactions" with these two, persuaded some military investigators to favor chloramphenicol for clinical use.<sup>103</sup> These and other studies by various members of this Army group have augmented the clinical and immunologic information of the disease. New epidemiologic observations have also accrued, notably the demonstration of *R. tsutsugamushi* in jungle rats and also in a species of mite (*Euschöngastia indica*) belonging to a genus different from the classical *Trombicula* vectors,<sup>104</sup> and reemphasis on the role of birds which for the first time were shown to be carrying infected mites.<sup>105</sup>

During and after World War II, vaccines were developed from two sources—yolk sacs of embryonated eggs and laboratory animal tissues. Though the problem was complicated by surprising antigenic heterogeneity of strains from various areas,<sup>106</sup> laboratory evidence raised hopes that human vaccination might be efficacious. Because the Vollner strain, recovered from a Naval patient in the Philippines,<sup>107</sup> appeared to have a broader antigenic character than some other laboratory strains, it was used at the Army Medical Department Research and Graduate School, Army Medical Center, Washington, D.C., in preparation of a rat lung-spleen vaccine and given an extensive field trial in Japanese farmers in endemic areas.<sup>108</sup> The disappointing conclusion was that this vaccine "was ineffective in preventing or modifying attacks on this disease."

An additional episode occurred in American occupation troops staging in two areas on the lower slopes of Mount Fuji, central Honshu Island, Japan, between August and October 1948. Of a total of 1,016 troops on maneuver, 24 were hospitalized with tsutsugamushi disease, confirmed serologically; at least an equal number of probably inapparent infections occurred in the same units as checked by random OX-K reactors.<sup>109</sup> It is likely that a new species of vector mite was involved.<sup>110</sup> Of special interest is this new focus thus discovered outside the classic endemic areas in Japan through the alertness of Army medical officers.

Since certain birds are known to become heavily infested with vector mites,<sup>111</sup> as well as to maintain rickettsiae in their tissues for more than 2 to 3 weeks,<sup>112</sup> it is strange that foci have not shown up during the occupation and subsequent combat operations in Korea. It appears probable that suitable ecologic conditions for survival of the vector mites are mostly lacking. Otherwise the infection should have become established there as readily as in the various islands along the Asiatic Coast.

<sup>103</sup> Bailey, C. A., Ley, H. L., Jr., Diercks, F. H., Lewthwaite, R., and Smadel, J. E.: Treatment of Scrub Typhus Evaluation of Chloramphenicol, Aureomycin, Terramycin, and Paraaminobenzoic Acid. *Antibiotics & Chemother.* 1: 16–30, April 1951.

<sup>104</sup> Traub, R., Frick, L. P., and Diercks, F. H.: Observations on the Occurrence of *Rickettsia tsutsugamushi* in Rats and Mites in the Malayan Jungle. *Am. J. Hyg.* 51: 269–273, May 1950.

<sup>105</sup> See footnote 98, p. 346.

<sup>106</sup> (1) See footnote 5, p. 278. (2) Bengtson, I. A.: A Serological Study of 37 Cases of Tsutsugamushi Disease (Scrub Typhus) Occurring in Burma and the Philippine Islands. *Pub. Health Rep.* 61: 887–894, June 1946. (3) Smadel, J. E., Ley, H. L., Jr., Diercks, F. H., and Traub, R.: Immunity in Scrub Typhus: Resistance to Induced Reinfection. *Arch. Path.* 50: 847–861, December 1950.

<sup>107</sup> See footnote 27, p. 291.

<sup>108</sup> Berge, T. O., Gauld, R. L., and Kitaoka, M.: A Field Trial of a Vaccine Prepared From the Vollner Strain of *Rickettsia tsutsugamushi*. *Am. J. Hyg.* 50: 337–342, November 1949.

<sup>109</sup> Annual Historical Report, 406th Medical General Laboratory. Tokyo, Honshu, Japan, 1948.

<sup>110</sup> Kuwata, T., Berge, T. O., and Philip, C. B.: A New Species of Japanese Larval Mite From a New Focus of Tsutsugamushi Disease in Southeastern Honshu, Japan. *J. Parasitol.* 36: 80–83, February 1950.

<sup>111</sup> See footnote 98, p. 346.

<sup>112</sup> Philip, C. B.: Scrub Typhus, or Tsutsugamushi Disease. *Scient. Month.* 69: 281–289, November 1949.





## CHAPTER XII

# Rocky Mountain Spotted Fever

*Glen M. Kohls, M.S.*

Although Rocky Mountain spotted fever was first recognized as a definite disease entity about 1890, the first published account was by an Army surgeon in 1896 concerning the disease in southern Idaho.<sup>1</sup> For many years, the disease was believed to be restricted to certain western States and adjoining Canadian provinces, but following proof in 1930 of the occurrence of the disease in the East,<sup>2</sup> it became apparent that spotted fever was endemic throughout much of the United States. The disease has been reported from all States except Maine and Vermont. It is known to be endemic in parts of Canada, Mexico, Panama, Colombia, and Brazil. Its distribution by counties in the United States up to January 1948 is shown on map 8.

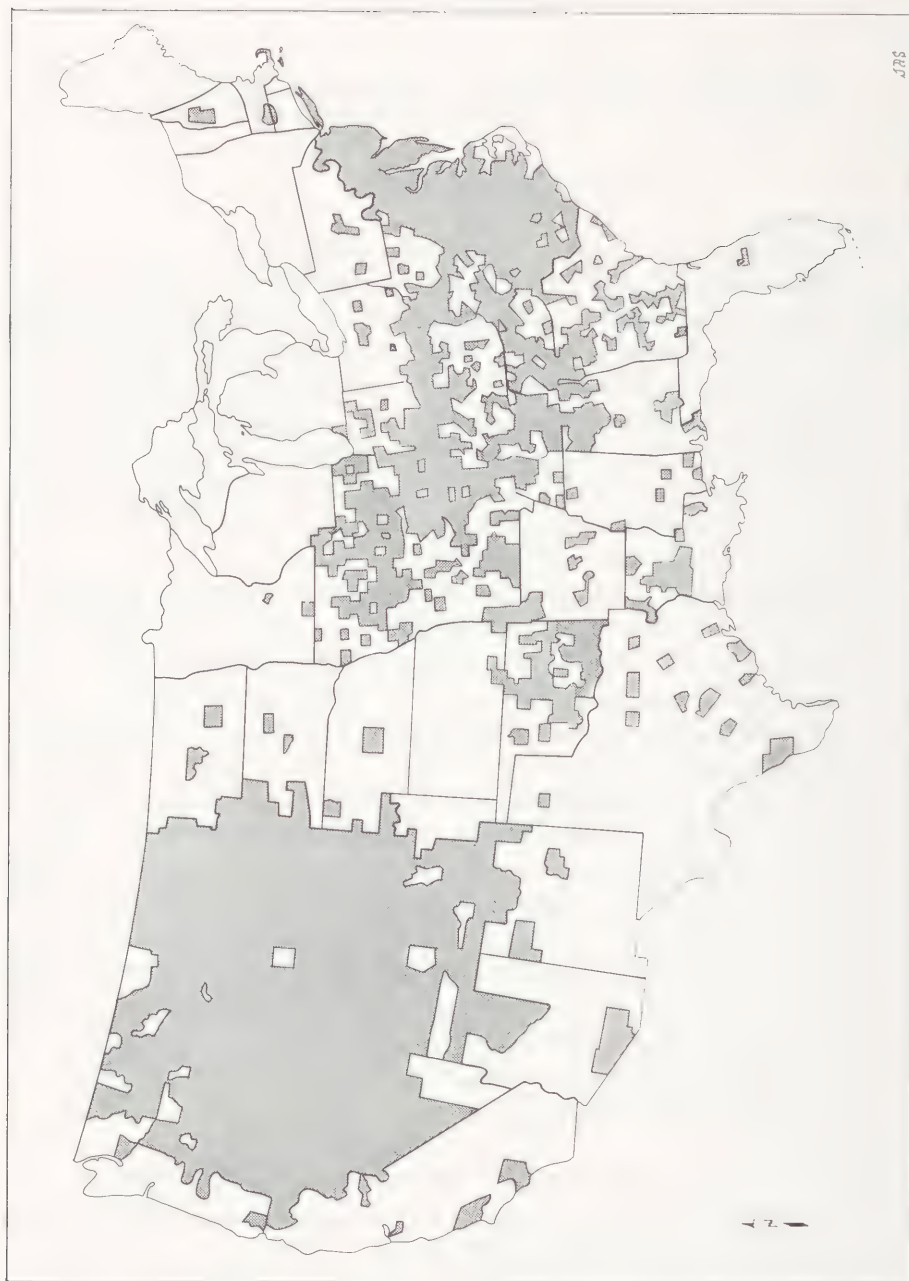
The etiologic agent of spotted fever, *Rickettsia rickettsi*, is resident in nature and is transmitted to man and to susceptible animals through the medium of infected ticks. The disease is characterized by onset with chills, headache, pain in the muscles and bones, fever which may continue for 2 to 3 weeks, and a rash which appears initially on the wrists and ankles and then spreads, in some cases, over the entire body. Nasopharyngitis is sometimes observed and was the working diagnosis on admission of several proved cases of spotted fever in troops in World War II. Clinical diagnosis of spotted fever is usually made by association of the rash, fever, history of tickbite or contact with ticks, geographic location, and season of the year. The serologic tests most frequently employed in diagnosis are the Weil-Felix and complement fixation tests. The latter is of particular value in differentiating spotted fever from endemic typhus and other rickettsial diseases.<sup>3</sup> In both tests, it is desirable and often necessary to test at least two serum samples—one taken early in the course of illness and the other after convalescence is well established—in order to demonstrate a significant rise in titer.

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<sup>1</sup> Report of The Surgeon General, U.S. Army. Washington: Government Printing Office, 1896, pp. 60–65.

<sup>2</sup> Badger, L. F., Dyer, R. E., and Rumreich, A.: An Infection of the Rocky Mountain Spotted Fever Type. Pub. Health Rep. 46: 463–470, February 1931.

<sup>3</sup> Plotz, H., and Wertman, K.: Scientific Apparatus and Laboratory Methods; the Use of the Complement Fixation Test in Rocky Mountain Spotted Fever. Science 95: 441–442, April 1942.



Map 8.—Distribution by counties of Rocky Mountain spotted fever in the United States (revised to January 1948)



## INCIDENCE

It could reasonably be assumed from available data on the prevalence of the disease in the United States, during the prewar years, that spotted fever would probably be of only minor importance from a military viewpoint in World War II, despite the fact that large numbers of individuals might be exposed to risk of infection coincident with training and other activities in tick-infested areas. The number of cases per year in the United States during the 1931-41 period ranged from 249 in 1931 to 544 in 1939.<sup>4</sup> The greatest number of cases reported for any one State during any one year was 127 for Montana in 1935.

For various reasons, both medical and statistical, the actual Army incidence can only be approximated. According to data furnished by the Medical Statistics Division, Office of The Surgeon General, based on sample tabulations of individual medical records, the number of admissions for the total U.S. Army for the 1942-45 period was 135, with 0.01 the annual rate per 1,000 mean strength. No oversea cases were reported.

Critical review by the author of all available records has reduced to 81 the total number of cases, probable and verified, that occurred in the Army during the 1941-45 period included in the present report. This total includes a single case in a prisoner of war infected in 1945 in Utah. It is quite probable that 81 does not represent the true incidence, but it is equally probable that it approximates it more closely than does 135. The annual incidence and the number of deaths for each of the 26 States in which cases occurred are shown in table 47, and for the service commands in table 48. It is of interest that 53, or more than one-half of the total number of cases, occurred in 1943. This is explainable, in part at least, by the relatively larger number of troops in training camps during that year.

Except for 1943, the number of cases that occurred in Army personnel—four in 1941, seven in 1942, nine in 1944, and eight in 1945—was insignificant in relation to the overall incidence of the disease in the United States. The extremes in number of cases per year during the war period, civilian and Armed Forces combined, ranged from 441 in 1942 to 502 in 1941.<sup>5</sup> Even in 1943 when 496 cases were reported, the 53 that occurred in Army personnel represented only 10.7 percent of the total. The fact that the Army cases were so distributed that 7 was the largest number that occurred in any State and 14 in any service command in any one year further minimized the importance of the disease as a military problem.

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<sup>4</sup> Parker, R. R., and Oliphant, J. W.: Rocky Mountain Spotted Fever. *In* Communicable Diseases. Philadelphia: Lea & Febiger, 1950, pp. 719-752.

<sup>5</sup> See footnote 4.

TABLE 47.—*Rocky Mountain spotted fever case incidence in U.S. Army troops by State, 1941-45*

State	1941-45		1941		1942		1943		1944		1945	
	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths
Alabama.....	6	0					3	0	2	0	1	0
California.....	3	1	1	0			2	1				
Colorado.....	5	0					5	0				
Delaware.....	1	0			1	0						
Georgia.....	2	1	1	1							1	0
Illinois.....	2	0	1	0							1	0
Kansas.....	1	0	<sup>1</sup> 1	0								
Kentucky.....	1	0							1	0		
Louisiana.....	4	1					3	1			1	0
Maryland.....	5	1			1	1	2	0	1	0	1	0
Massachusetts.....	1	0					1	0				
Mississippi.....	3	0					2	0	1	0		
Missouri.....	2	1			1	1	1	0				
Montana.....	1	0									1	0
New Jersey.....	1	1			1	1						
New York.....	1	0					1	0				
North Carolina.....	4	0			1	0	3	0				
Oregon.....	5	0					5	0				
Oklahoma.....	5	2					5	2				
South Dakota.....	1	0									1	0
Tennessee.....	7	0					7	0				
Texas.....	7	2			<sup>2</sup> 1	1	5	1	1	0		
Utah.....	4	0					3	0			1	0
Virginia.....	6	2			1	0	3	2	2	0		
Washington.....	2	0					2	0				
Wyoming.....	1	1							1	1		
Total.....	81	13	4	1	7	4	53	7	9	1	8	0

<sup>1</sup> May have been infected in Arkansas while on maneuvers.<sup>2</sup> May have been infected in Illinois while on furlough.TABLE 48.—*Rocky Mountain spotted fever case incidence in U.S. Army troops by service command, 1941-45*

Service command	1941-45		1941		1942		1943		1944		1945	
	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths	Number of cases	Number of deaths
First.....	1	0					1	0				
Second.....	2	1			1	1	1	0				
Third.....	12	3			3	1	5	2	3	0	1	0
Fourth.....	21	1	1	1	1	0	14	0	3	0	2	0
Fifth.....	1	0							1	0		
Sixth.....	2	0	1	0							1	0
Seventh.....	10	2	<sup>1</sup> 1	0	1	1	6	0	1	1	1	0
Eighth.....	17	5			1	<sup>2</sup> 1	14	4	1	0	1	0
Ninth.....	15	1	1	0			12	1			2	0
Total.....	81	13	4	1	7	4	53	7	9	1	8	0

<sup>1</sup> May have been infected in Eighth Service Command (Arkansas).<sup>2</sup> May have been infected in Sixth Service Command (Illinois).

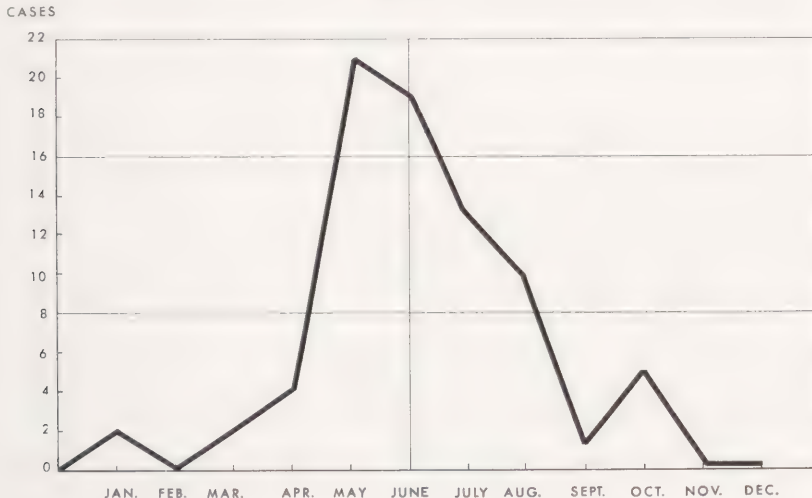
# MORTALITY

Of the 77 Army cases that occurred during the 1942-45 period, 12 were fatal, giving a case fatality rate of 15.58 percent. For troops in the United States, the annual mortality rate per 100,000 mean strength was 0.08 and for the total Army, 0.05. On the basis of 13 deaths among 81 cases during the 1941-45 period, the case fatality rate was 16.05 percent as compared with a rate of 18.89 percent for the general population during the 1931-46 period.<sup>6</sup> The close agreement of the Army case fatality rate with that for the general population supports the view that the true incidence in the Army was closer to 77 cases than to 135 during the 1942-45 period. The diagnosis of Rocky Mountain spotted fever was verified or reasonably well established for all of the deaths reported.

# SEASONAL DISTRIBUTION

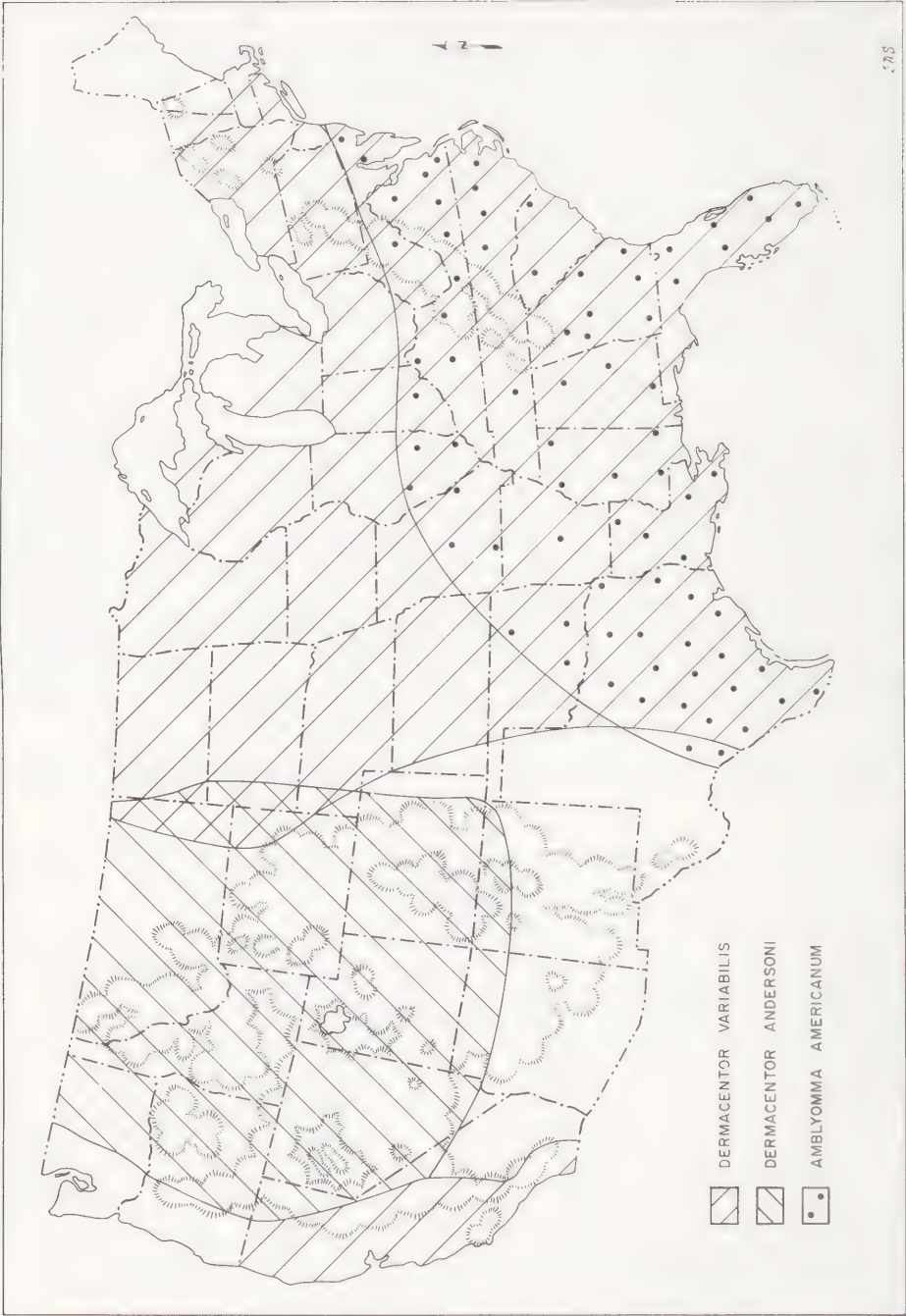
Distribution by month of 77 of the 81 cases that occurred during 1941-45 is shown in chart 21. Four cases are omitted here because of lack of information as to the month in which they occurred. The seasonal incidence is correlated with the active periods of the particular developmental stages of the three vector species of ticks responsible for transmission of the disease to man. The ranges of these species in the United States are shown in map 9. Except in rare instances, the adults of the Rocky Mountain wood tick, *Dermacentor andersoni*, and of the American dog tick, *Dermacentor variabilis*, are the only stages of these two ticks that bite man. They are active chiefly during the

CHART 21.—Seasonal incidence of 77 Army cases of Rocky Mountain spotted fever during 1941-45



<sup>6</sup> See footnote 4, p. 351.





MAP 9.—Ranges of the three known vectors of Rocky Mountain spotted fever to man in the United States.

spring and early summer months, but the activity of *D. variabilis* adults begins later and continues later than in the case of *D. andersoni*. The immature stages as well as the adults of the Lone Star tick, *Amblyomma americanum*, attack man, and one or more of these developmental stages may be active throughout the year in the warmer parts of the region where this species occurs. However, this species has been definitely incriminated as the responsible vector in only a few cases, none of which are known to have involved Army personnel. It was an important pest species in some southern training areas, notably Camp Bullis near Fort Sam Houston, Tex., where it was also considered to be the probable vector of Bullis fever.<sup>7</sup>

## PREVENTION

Since control of the tick vectors of Rocky Mountain spotted fever was not feasible, except perhaps under certain highly localized and special conditions, only two prophylactic measures were recommended—personal precautions and vaccination.<sup>8</sup>

**Personal precautions.**—Emphasis was placed on this measure. Individuals were instructed to avoid tick-infested areas if possible. Ticks were to be removed from the clothing and body at least once a day and routinely at night before retiring. Attached ticks were to be removed gently to avoid breaking off the mouth parts. This was to be done with tweezers or with cotton saturated with iodine, not with the bare fingers. The site of the tick bite was to be painted with iodine, and the hands were to be thoroughly washed after handling ticks, especially after removing ticks from animals. Dogs were to be deticked at frequent intervals.

A means of preventing tick attachment was obviously needed. Wartime mosquito repellents were unsatisfactory or of little value for this purpose. A review of the search for safe and effective tick repellents during and following the war is not pertinent here, but it may be noted that several have been developed which offer considerable promise.<sup>9</sup>

**Vaccination.**—The policy was adopted early in the war that mass vaccination of troops against Rocky Mountain spotted fever would not be undertaken,<sup>10</sup> and as a result, vaccination was practiced only to a limited extent. Prewar experience had indicated that the attack rate was low even in areas where the disease occurred most frequently. Protection afforded by vaccination was likely to be incomplete and of short duration, but could be counted

<sup>7</sup> Brennan, J. M.: Field Investigations Pertinent to Bullis Fever. Texas Rep. Biol. & Med. 3: 204–226, 1945.

<sup>8</sup>(1) Circular Letter No. 33, Office of The Surgeon General, U.S. Army, 2 Feb. 1943, subject: Treatment and Control of Certain Tropical Diseases. (2) War Department Technical Bulletin (TB Med) 114, 9 Nov. 1944.

<sup>9</sup>(1) Brennan, J. M.: Field Tests With Tick Repellents. Pub. Health Rep. 63: 339–346, 12 Mar. 1948. (2) Cole, M. M., and Smith, C. N.: Tick Repellent Investigations at Bull's Island, S.C., 1948. J. Econ. Entomology 42: 880–883, 1949.

<sup>10</sup> Long, Arthur P.: The Army Immunization Program. In Medical Department, United States Army. Preventive Medicine in World War II. Volume III. Personal Health Measures and Immunization. Washington: U.S. Government Printing Office, 1955, pp. 333–335.

on to modify the course of infection and to insure recovery and more rapid convalescence.<sup>11</sup>

The policy adopted was that of limited vaccination, largely of personnel in areas where contact with ticks was unavoidable and where danger of infection seemed to be particularly great. In this category were patrols, guards, and other personnel operating in heavily infested areas where there appeared to be a definite risk of contracting the disease. The number of individuals who received the vaccine is not known, but an estimate may be made from the amount of vaccine which was made available to the Army by the U.S. Public Health Service. During 1942, enough vaccine was furnished to vaccinate 20,000 individuals. Since this amount appeared to be excessive in view of the limited vaccination policy, the U.S. Public Health Service was requested to allot a total of 50,000 cc. per year in subsequent years. This was enough for about 12,000 persons on the basis of the prevailing dosage schedule of 4 cc. given in two doses of 2 cc. each, with an interval of 5 to 7 days, or for about 16,000 persons when the dosage was changed in 1944 to 3 doses of 1 cc. each. Suballotments were made to the several service commands, and the policy of limiting vaccination to certain troops in areas regarded as particularly hazardous was emphasized. The quantity of vaccine distributed in 1943 was consequently reduced to an amount sufficient to vaccinate about 10,000, and in 1944 only about 3,500 persons.<sup>12</sup> During 1945, however, enough vaccine for approximately 16,000 persons was distributed—the increase over 1944 being due largely to vaccination of prisoners of war in areas where the danger of infection appeared to be significant.

So far as is known, there were no cases in vaccinated individuals. This was probably an indication of the low attack rate rather than evidence of the efficacy of the vaccine in prevention of the disease.

With the postwar discovery of promising tick repellents and effective therapeutic agents, it would appear that Rocky Mountain spotted fever will be even less of a problem among Army personnel in the future than it has been in the past.

<sup>11</sup> Parker, R. R.: Rocky Mountain Spotted Fever: Results of Fifteen Years' Prophylactic Vaccination. *Am. J. Trop. Med.* 21: 369-383, May 1941.

<sup>12</sup> Letter, R. R. Parker, Director, Rocky Mountain Laboratory, Hamilton, Mont., to Lt. Col. J. W. R. Norton, MC, Acting Director, Epidemiology Division, Office of The Surgeon General, U.S. Army, 1 June 1944.



## CHAPTER XIII

# Yellow Fever

*Stanhope Bayne-Jones, M.D.*

No case of yellow fever was reported among military personnel during the period of participation of the United States in World War II. Indeed, no cases occurred in military personnel in either the years immediately preceding 7 December 1941, or the years subsequent to 2 September 1945, to the date of this writing in November 1951. During these 10 years, there was no spread of yellow fever attributable to any component of the Military Establishment of the United States. As the risks were considerable, and exposure to infection is now recognized to have been greater than was known during the war, the nonoccurrence of the disease among military personnel and the limiting of yellow fever to endemic regions of Africa, South America, and Central America direct attention particularly to the control measures that were applied to safeguard troops and civilian populations.

## COOPERATIVE RESPONSIBILITIES IN THE UNITED STATES AND ABROAD

The control measures directed against yellow fever were various and extensive. Their application involved complex national and international arrangements which placed unexpected responsibilities upon the Office of The Surgeon General. This Office dealt with the problems chiefly through its Preventive Medicine Service under the direction of Lt. Col. (later Brig. Gen.) James S. Simmons, MC. In carrying out its mission, the Preventive Medicine Service, with due authorization, developed and maintained contact with numerous commissions, scientific bodies, civilian and governmental agencies, including, among others, the U.S. Public Health Service, the Department of State, the British Inter-Departmental Committee on Yellow Fever Control, the Government of India, the Government of Egypt, the Government of Brazil, and among military commands, particularly those in the Middle East, North Africa, Middle Atlantic, Caribbean, China-Burma-India, and Pacific Ocean areas. During one stage, direct contact with the General Staff was required.

The main point of listing these relationships is to indicate that the total operation was a good illustration of two principles of military preventive medicine. The first, as pointed out in the history of the Medical Department

of the Army in World War I,<sup>1</sup> is that while most of the functions of the Office of The Surgeon General are concerned with technical, professional, and administrative matters under the command of The Surgeon General, the functions of preventive medicine concern the administration of the Army as a whole, with responsibility resting finally upon military commanders. The second principle, valid in peace as in war, is that in dealing with a disease of hemispheric distribution and potentiality for worldwide spread an effective preventive program must secure international understanding and acceptance, through direct contact between experts, and must have the informed support of the highest governmental and military authorities.

These principles were recognized in the planning stages of the Army's yellow fever prevention program. Nevertheless, they were overlooked in some phases of operations, with resultant delays in carrying out portions of the program, and hindrance of movement of troops, civilians, and supplies. In the opinion of this author, these difficulties were attributable largely to the prolonged negotiations that were required to secure the direct international communication which was necessary for the harmonizing of conflicting regulations and diverse special interests. The necessity for finding the way through a maze of channels of slow-moving communication need not be repeated in the future.

Before proceeding with an account of the control measures and some of the results of their application, it is desirable to review briefly the history of yellow fever and its conquest. From this, it will be seen that all of the essential information was available when the United States entered the war in December 1941.

## KNOWLEDGE OF YELLOW FEVER AND ITS CONTROL BEFORE WORLD WAR II

Ever since its recognition as a distinct disease, in the 18th century, yellow fever has been regarded as one of the great plagues of the world and as a pestilence of enormous potential menace. A history of the origin and effects of yellow fever, by Henry Rose Carter,<sup>2</sup> published in 1931, contains abundant evidence of the disastrous course of yellow fever. The account of the influence of yellow fever upon the Cuban Campaign in 1898-1900 and upon the construction of the Panama Canal is a familiar story. Fortunately, for all seeking further knowledge of the modern conquest of this disease, there was published in 1951 under the editorship of George K. Strode, a superb volume entitled "Yellow Fever."<sup>3</sup> This book presents particularly the part played by the International Health Division of the Rockefeller Foundation, N.Y.,

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<sup>1</sup> The Medical Department of the United States Army in the World War. Washington: Government Printing Office, 1923, vol. I, pp. 245-285.

<sup>2</sup> Carter, Henry Rose: *Yellow Fever. An Epidemiological and Historical Study of Its Place of Origin.* Baltimore: The Williams & Wilkins Co., 1931.

<sup>3</sup> Strode, George K. (editor): *Yellow Fever.* 1st edition. New York: McGraw-Hill Book Co., Inc., 1951.

during the past 30 years in the worldwide campaign against yellow fever. At the same time, it deals adequately with the earlier work of Maj. Walter Reed, MC, and Maj. Gen. William C. Gorgas, and treats the whole subject broadly. It is appropriate in referring to this volume to acknowledge again, on behalf of The Surgeon General, the tremendous service rendered during the war by the International Health Division of the Rockefeller Foundation in providing not only vast quantities of yellow fever vaccine, but also the personal services of its Director, Dr. Wilbur A. Sawyer, and of other officers and staff members of the Division. From the Division, the Army received technical information and advice which enabled the United States to reach satisfactory agreements with Great Britain, India, Egypt, and other countries with regard to yellow fever quarantine and related matters.

In his chapter on "Landmarks in the Conquest of Yellow Fever," in the volume "Yellow Fever," just cited, Andrew J. Warren shows that by 1940 all the knowledge essential to a modern control program had been established. In summary, his main points are as follows:

1. The proof provided by the U.S. Army Yellow Fever Board in Cuba, under Maj. Walter Reed, in 1900-1901, that yellow fever is transmitted by a mosquito (*Aedes aegypti*) and that the causative agent is ultramicroscopic and filtrable. The final proof that the causative agent of yellow fever is a virus was furnished in 1927 by A. Stokes, J. H. Bauer, and N. P. Hudson.

2. The discovery in 1927 by A. F. Mahaffy and J. H. Bauer of a susceptible "laboratory animal" (*Macaca rhesus* monkey), and the discovery in 1930 by Max Theiler that white mice are susceptible to yellow fever virus.

3. The development of the mouse protection test by M. Theiler in 1931—a test found to be indispensable for epidemiologic surveys as well as for other immunologic investigations.

4. The development of successful techniques for the eradication of the urban vector, *A. aegypti*, applying particularly antimosquito methods for "species sanitation," as advocated by F. L. Soper and others.

5. The discovery of jungle yellow fever and its role in the epidemiology of the disease. This resulted essentially from the work of Soper and his associates in Brazil in 1932, and the reports of various investigators, among whom were C. B. Philip and J. H. Bauer. From 1928 through subsequent years, they reported that several species of *Aedes*, *Haemagogus*, *Eretmapodites*, and *Taeniorhynchus* mosquitoes were capable of transmitting yellow fever. In the course of these studies, it was shown that, in addition to mosquitoes, ticks of several genera and bird mites can be artificially infected with yellow fever virus. Apparently, ticks and mites cannot transmit the infection to man, but the significance of the susceptibility of these arthropods is not yet fully known.

6. The development of a relatively simple and practicable method of vaccination against yellow fever, based upon the work of M. Theiler<sup>4</sup> and H. H. Smith in 1937, with the 17D strain (Asibi strain) of yellow fever virus.

<sup>4</sup> In recognition of his great contribution in this field, Theiler was awarded the Nobel Prize in 1951.—S. B.-J.



Problems of the control of yellow fever are complicated by the geographic distribution of the chief mosquito vector of the urban form of the disease, *A. aegypti*, throughout vast areas where yellow fever occurs and vast areas in which it has not yet occurred.

### Geographic Distribution of *Aedes aegypti*

The distribution of *A. aegypti* is shown by the shaded areas in map 10—a reproduction of the map prepared by Lavier and Stefanopoulo<sup>5</sup> based largely on the monograph of Kumm.<sup>6</sup> The habitat of this mosquito extends in a belt around the world between the parallels of 45° north latitude and 40° south latitude. This huge area includes the known endemic regions of yellow fever in Central and South America and Africa, regions in which epidemics of yellow fever have occurred in the past, as in the United States, and in countries in which yellow fever has not occurred; namely, India, Burma, Indochina, Malaya, New Guinea, Australia, other islands in the South and Southwest Pacific, the east coast of China, Formosa, Korea, and Japan. In commenting on this, Dr. R. M. Taylor of the International Health Division of the Rockefeller Foundation in a letter to this author, dated 6 January 1950, wrote:

\* \* \* in recent years, due to the anti-*aegypti* campaign in South America much of the area shown on the map has now been ridded of this mosquito. Indeed, with the exception of parts of Central America and the United States, and possibly parts of Cuba and certain of the Virgin Islands, the prevalence of this mosquito has been reduced to a point that would not permit yellow fever virus, although introduced, to assume epidemic proportions.

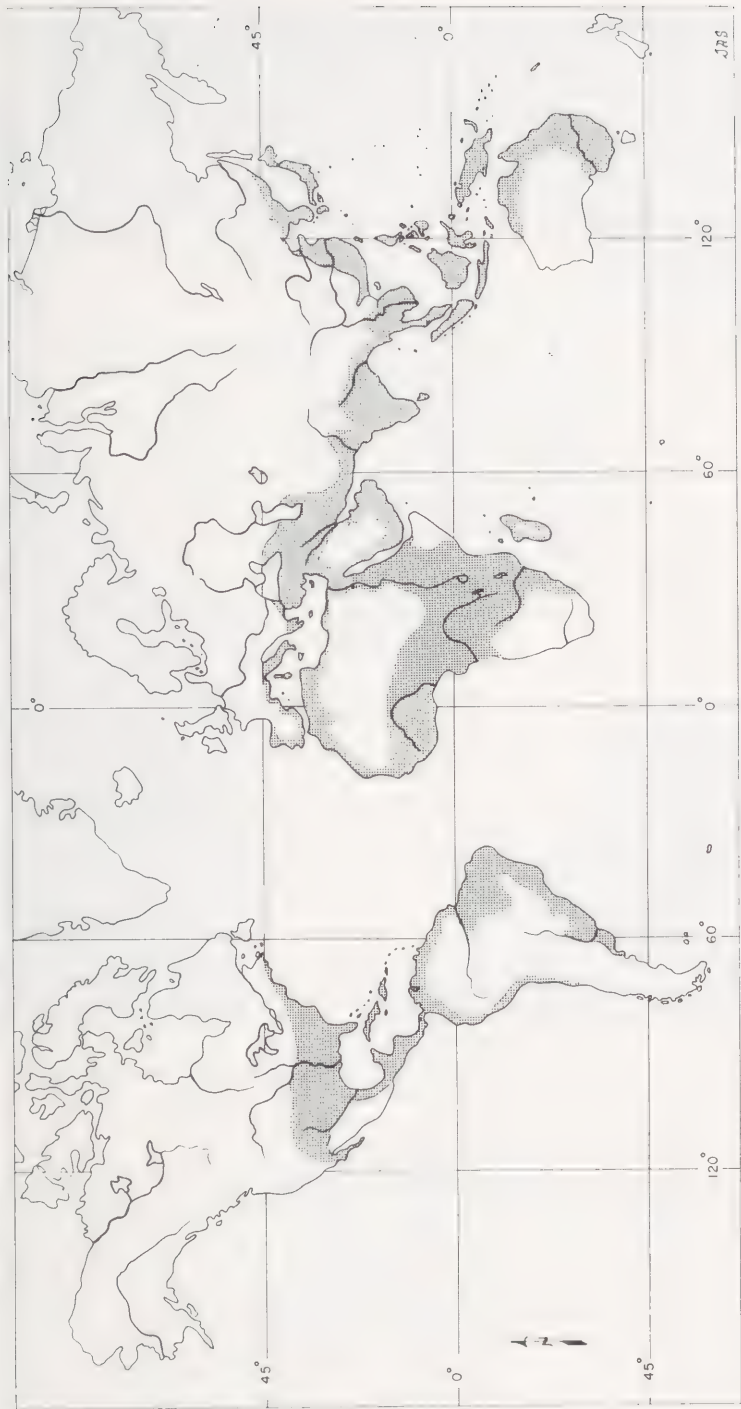
Experimental tests<sup>7</sup> have shown that *A. aegypti* from any of these regions can be infected with the virus of yellow fever and can transmit the infection. There is every reason to assume that the human inhabitants of these areas are susceptible to yellow fever, although the proof of this has not yet been brought forth. The occurrence of *A. aegypti* in densely populated areas thus far exempt from yellow fever presents the menace of the disease to the Far East. For many years, this has been the reason for dreading that epidemics of yellow fever of unprecedented destructiveness might occur among the millions of nonimmunes in India and other countries, if the infection were introduced among them by imported cases of yellow fever or by infected mosquitoes. Protection against this risk has been an objective of major concern to the Indian Government ever since 1903 when Manson called attention to the health hazards to which the opening of the Panama Canal exposed the Far East. It has been the basis of the long-continued rigorous quarantine regulations of the Indian

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<sup>5</sup> Lavier, G., and Stefanopoulo, G. J.: *Fièvre Jaune*. L'Encyclopédie Médico-chirurgicale, 2d edition, Paris, 12-1946C.

<sup>6</sup> Kumm, H. W.: The Geographical Distribution of the Yellow Fever Vectors. Am. J. Hyg. Monograph Series No. 12, 1931.

<sup>7</sup> Whitman, L.: The Arthropod Vectors of Yellow Fever. In *Yellow Fever* (George K. Strode, editor). 1st edition. New York: McGraw-Hill Book Co., Inc., 1951.



MAP 10.—Geographic distribution of *Aedes aegypti*, shown by shaded areas. (From Lavier, G., and Stefanopoulo, G. J.: *Fièvre jaune*. L'Encyclopédie Médico-chirurgicale, 2d edition, Paris, 12-1946C.)

Government, which in turn have influenced the regulations of the British Inter-Departmental Committee on Yellow Fever Control<sup>s</sup> and the quarantine regulations of various colonies of equatorial Africa, and of Egypt.

The distribution of this mosquito, *A. aegypti*, determined international and Army policies with respect to yellow fever control. The possibility, however remote, that the Japanese might introduce yellow fever into the Pacific area had an influence in 1941 upon the decision to adopt yellow fever vaccination for the U.S. Army.

### Endemic Areas

The endemic areas of yellow fever in the Americas and Africa (maps 11 and 12) as delineated in the 28 June 1950 issue of the *Weekly Epidemiological Record* of WHO (World Health Organization) are as follows:

**The American Endemic Yellow Fever Area.**—This area is bounded by a line beginning on the Pacific Coast of Colombia at the 5° N. parallel of latitude and extending east along that parallel of latitude to the eastern slopes of the Central Cordillera to an elevation of 2,000 metres; thence southward along the eastern slopes to the Central Cordillera and the Andes Mountains, at the same elevation to the boundary of Bolivia and Argentina; thence eastward and northward along the southern and eastern boundaries of Bolivia to the 15° S. parallel of latitude; thence eastward along that parallel of latitude to the western boundary of the State of Goiás; thence northward along that boundary and the western boundary of the State of Maranhão to the Atlantic Coast; thence along the Atlantic and Caribbean coasts of America to the eastern boundary of Costa Rica; thence along that boundary to the Pacific Coast and thence along the Pacific Coast of Panama and Colombia to the 5° N. parallel of latitude. In addition, the Ilhéus and Itabuna Districts in the State of Bahia in Brazil bounded on the north by the River Contas, on the west by the 40° W. meridian of longitude, on the south by the River Pardo and on the east by the Atlantic Ocean are included in the endemic yellow fever area. The ports of Belém and Manaus in Brazil, Cayenne in French Guiana, Paramaribo in Surinam, Georgetown in British Guiana, the Caribbean ports of Venezuela and Colombia, the cities of Caracas in Venezuela and Bogotá in Columbia, together with the ports of the Republic of Panama and the Panama Canal Zone are excluded from the endemic yellow fever area. The continued exclusion of these ports and cities is, however, contingent on their maintenance of an *Aedes aegypti* index not exceeding 1 percent, as reported quarterly to WHO.

**The African Endemic Yellow Fever Area.**—From the mouth of the River Senegal along that river eastward to the 15° N. parallel of latitude; thence eastward along that parallel to the eastern border of the Anglo-Egyptian Sudan; thence northward along the northwestern boundary of Eritrea to the Red Sea Coast; thence southward along the eastern coast of Africa to the northern boundary of the French Somali Coast; thence along that boundary successively westward, southward and eastward to the eastern coast of Africa and thence along this coast to the southern boundary of the Protectorate of Kenya; thence westward along that boundary and the southern boundary of Kenya Colony to its junction with the southern border of the Uganda Protectorate; and thence along this and the eastern border of Ruanda Urundi and of the Belgian Congo to the 10° S. parallel of latitude; thence westward along that parallel to the west coast of Africa; thence northward along the west coast of Africa to the mouth of the River Senegal; including the islands of the Gulf of Guinea; the whole territory of Nyasaland Protectorate, the Barotse Province and the Balovale District in the Western Province of Northern Rhodesia, together with

<sup>s</sup> Inter-Departmental Committee on Yellow Fever Control. 3d Interim Report. Miscellaneous No 503A, London: Colonial Office, September 1942.





MAP 11.—Endemic yellow fever area in South America. (From *Weekly Epidemiological Record*, World Health Organization, 25th year. No. 26, 28 June 1950.)

the territory to the South of Barotseland lying between the  $23^{\circ}$  and  $25^{\circ}$  E. meridians of longitude down to the  $21^{\circ}$  S. parallel of latitude, are also included in the endemic area. The port of Massawa in Eritrea and an area 10 kilometres in radius from the centre of the town of Asmara in Eritrea, as well as the territory of the French Somali Coast, including the port of Djibouti, are excluded from the endemic area. The continued exclusion of these areas, is, however, contingent on their maintenance of an *Aedes aegypti* index not exceeding 1 percent in the port of Massawa, in and around Asmara and in the port of Djibouti, as reported quarterly to WHO.

In 1940, the endemic area of yellow fever in Central and South America (map 11) was clearly defined, and protective vaccination and other measures



MAP 12.—Endemic yellow fever area in Africa. (From *Weekly Epidemiological Record*, World Health Organization, 25th year. No. 26, 28 June 1950.)

of protection for troops stationed in or passing through those areas were an easily demonstrable necessity. As pointed out by Col. Phillip T. Knies, MC,<sup>9</sup> however, numerous difficulties arose in relations with the Brazilian Government over regulations designed to prevent the introduction of possibly infected mosquitoes into Natal and other eastern Brazilian ports by airplanes.

<sup>9</sup> Knies, Phillip T.: Foreign Quarantine. In Medical Department, United States Army. *Preventive Medicine in World War II*, Volume II. Environmental Hygiene. Washington: U.S. Government Printing Office, 1955, pp. 271-324.

The severe outbreak of yellow fever in the Anglo-Egyptian Sudan in 1940<sup>10</sup> alarmed the world, as it indicated virulent extension of the disease toward the East Coast of Africa and possibly to Egypt. It is to be recalled that in 1941 and 1942, the success of the German armies in North Africa forced an urgent effort by the United States to establish air transport routes across equatorial Africa, from west to east, as supplement to the Mediterranean-Suez route. Hence, all precautions of vaccination and quarantine were applicable to these areas. At the time when they were instituted, the full disclosure of the endemic African yellow fever area (map 12) had not been made because the immunologic surveys of British organizations in collaboration with the International Health Division of the Rockefeller Foundation were still in progress. Map 12 shows that the results of these surveys made from 1942 to 1950 extended the area both eastward to the coasts of Kenya, Somalia, Ethiopia, Somaliland, Eritrea, to the southern border of the Belgian Congo, and to an area in Angola, Northern Rhodesia, and Bechuanaland. It is on the basis of these disclosures, and the more recent knowledge of the prevalence of yellow fever in West Africa, that the statement was made earlier in this chapter that the exposure to yellow fever of military and associated personnel had been greater than was known at the time. In support of this opinion, the following is quoted from a letter dated 9 January 1950 from Dr. John C. Bugher of the staff of the International Health Division of the Rockefeller Foundation:

Most of these outbreaks and especially the ones in Gold Coast and Nigeria were in regions in which the aircraft in the ferrying operations made their chief stops. In my opinion, the risks of contact with yellow fever during the war were considerably greater than were thought at the time the precautionary measures were established and the fact that no cases occurred among American personnel and there was no evidence of any spread of the disease due to air transport speaks for the efficiency of the measures in force at the time.

With this review and general statement as a background, it is appropriate now to return to an account of activities and events in the Army's program of prevention and control of yellow fever.

## DEVELOPMENT ON CONTROL PROGRAM IN THE ARMY

On 24 February 1940, when Colonel Simmons was assigned as Chief, Preventive Medicine Section (later Service),<sup>11</sup> Office of The Surgeon General, the war in Europe had been in progress for about 6 months and the possible involvement of the United States in a war that might become global was anxiously considered by thoughtful people. The possible need for immunization of military personnel against yellow fever and the need to place the military forces in position to comply with international quarantine regulations, par-

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<sup>10</sup> Kirk, R.: Epidemic of Yellow Fever in Nuba Mountains, Anglo-Egyptian Sudan. *Ann. Trop. Med.* 35: 67-112, October 1941.

<sup>11</sup> Office Order No. 20, Office of The Surgeon General, U.S. Army, 26 Feb. 1940.



ticularly those of Great Britain and India, were foreseen by Colonel Simmons. He began at once to develop a program for recommendation to The Surgeon General for adoption for the Army. He was exceptionally well equipped to do this through his scientific researches, experience, and personal associations with the members of Army and civilian groups that had been engaged for years in work on yellow fever.

It is important to note that the program was developed not exclusively by Army personnel, but, in accordance with traditions stemming from Brig. Gen. George M. Sternberg, by consultation and collaboration with civilian and governmental agencies and by securing the patriotic assistance of the ablest men in the field.

The first formal conferences on the subject were held at the request of Colonel Simmons in May and June 1940 by the Committee on Chemotherapeutic and Other Agents<sup>12</sup> and the Advisory Committee on Tropical Diseases<sup>13</sup> of the National Research Council. Thus, before the entry of the United States into the war, a pattern of comprehensive collaboration was established. Throughout the war, there was no deviation from this design. By following it, incalculably valuable assistance and strength were woven into the preventive medicine structure of the Army.

The main elements of the yellow fever control program of the Army were as follows: (1) Exact, authoritative, current, technical, and epidemiologic information; (2) vaccination against yellow fever; (3) antimosquito measures, both general and specific, including disinsectization of aircraft, ships, and other transport; (4) quarantine; and (5) adjustment of conflicting regulations relative to yellow fever.

### Vaccination

Vaccination against yellow fever has been discussed in detail by Col. Arthur P. Long, MC.<sup>14</sup> The volume "Yellow Fever" contains not only a chapter on this subject but also a complete presentation of the work of the International Health Division of the Rockefeller Foundation on investigations of yellow fever virus, and the development and use of the modified 17D (Asibi) strain, which was the virus-vaccine adopted for the Army on 30 January 1941. These comprehensive publications make it unnecessary to review in this place the scientific and administrative aspects of the program of yellow fever vaccination in the Army. The success of the program has been discussed in previous paragraphs of this chapter.

Although a detailed report of the outbreak of hepatitis associated with vaccination against yellow fever is made unnecessary by other articles on that

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<sup>12</sup> Minutes, Meeting, Committee on Chemotherapeutic and Other Agents, National Research Council, Division of Medical Sciences, 28 May 1940.

<sup>13</sup>(1) Minutes, Meeting, Advisory Committee on Tropical Diseases of the National Research Council, 19 June 1940. (2) Minutes, Meeting, Subcommittee on Tropical Diseases, Division of Medical Sciences, National Research Council, 30 July 1940.

<sup>14</sup> Long, Arthur P.: The Army Immunization Program. In Medical Department, United States Army. Preventive Medicine in World War II. Volume III. Personal Health Measures and Immunization. Washington: U.S. Government Printing Office, 1955, pp. 271-343.

subject, nevertheless, a summary of the experience, with some additional material, is appropriate in this place.

### Outbreak of Postvaccination Hepatitis

In 1942, the yellow fever vaccination program was nearly wrecked by the Army-wide outbreak of hepatitis (jaundice) which followed the administration of certain lots of the vaccine prepared by the International Health Division of the Rockefeller Foundation. This outbreak of hepatitis has been fully described by Colonel Long,<sup>15</sup> by Paul and Gardner,<sup>16</sup> and by Walker.<sup>17</sup> At the time of the outbreak of hepatitis, the Army Epidemiological Board was in operation. Full use was made of the Board and of some of its Commissions to attack the problem in supplementation of the work of Army personnel in military camps and laboratories. Expert advice on policy and procedures was thus obtained. From the investigations undertaken by the Board and Commissions, and continued since 1942, an abundance of new scientific information about hepatitis has been obtained, of great value to civilian and military medicine. For many details, the reader is referred, in addition to the sources just cited, to the monographic publications of W. A. Sawyer and associates.<sup>18</sup>

The outbreak of hepatitis, called simply "jaundice" at the start, began in February 1942, almost simultaneously among troops at stations far apart—in the continental United States, in Latin America, in Hawaii, in various islands of the Pacific, and in Burma. It occurred later among troops in Europe, in North Africa, in Alaska, and in many other locations.

The peak of the outbreak of postvaccinal hepatitis was reached in the last week of June 1942, and the whole was contained within the year 1942. From late February to 31 December 1942, there were reported 49,111 cases of hepatitis with 81 deaths. It is known to this author and to others that there were many unreported cases of mild or nonicteric hepatitis (possibly several thousand) following the administration of certain lots of yellow fever vaccine.

On the basis of previous knowledge and circumstantial probabilities, it was decided in April 1942, at the Office of The Surgeon General, that this outbreak of hepatitis was due to the small amount (0.04 cc.) of human serum which was in each dose of vaccine. The previous knowledge about "serum jaundice," or hepatitis, associated with yellow fever vaccine containing human serum was derived from experiences with this type of vaccine in Africa and Brazil before 1942. The circumstantial evidence that the vaccine was icterogenic was provided by a great mass and variety of epidemiologic data from

<sup>15</sup> See footnote 14, p. 366.

<sup>16</sup> Paul, John R., and Gardner, Horace T.: Viral Hepatitis. In Medical Department, United States Army. Preventive Medicine in World War II. Volume V. Communicable Diseases. Washington: U.S. Government Printing Office, 1960, pp. 411-462.

<sup>17</sup> Walker, D. W.: Some Epidemiological Aspects of Infectious Hepatitis in the U.S. Army. *Am. J. Trop. Med.* 25: 75-82, March 1945.

<sup>18</sup> Sawyer, W. A., Meyer, K. F., Eaton, M. D., Bauer, J. H., Putnam, P., and Schwentker, F. F.: Jaundice in Army Personnel in the Western Region of the United States and Its Relation to Vaccination Against Yellow Fever. Part I. *Am. J. Hyg.* 39: 337-430, May 1944, and Parts II, III, and IV. *Am. J. Hyg.* 40: 35-107, July 1944.

Army posts and camps. Preponderantly, only the vaccinated had hepatitis and jaundice while the nonvaccinated in the same location were not affected. The curves or forms of the outbreaks of hepatitis occurring from 90 to 120 days after vaccination were small replicas of the vaccination schedules, a simple relationship which this author called "pictorial epidemiology." The experimental proof that a certain lot of vaccine was icterogenic was not provided until 2 years later when human volunteers, injected with this material, developed hepatitis after the expected long incubation period. Although a long time was required to assemble all the evidence, the case was considered to be sufficiently established by 15 April 1942 (about 6 weeks after the beginning of the outbreak) to require discontinuation, at least temporarily, of the serum-containing vaccine prepared by the International Health Division Laboratories of the Rockefeller Foundation, and to use instead the aqueous-base, serum-free vaccine prepared by the Rocky Mountain Laboratory, Hamilton, Mont., of the U.S. Public Health Service. The International Health Division Laboratories of the Rockefeller Foundation quickly turned to the manufacture of aqueous-base, serum-free vaccine, and large quantities of this vaccine were then produced for use by the Armed Forces. Thereafter, there were no proved cases of hepatitis associated with the administration of this vaccine.

As it had been known that human serum might contain the virus of hepatitis, it was believed that by careful selection of donors and by heating the serum at 56° C. for one-half hour, the risk would be greatly reduced and the virus, if present, would be inactivated. Both precautions had been observed. Neither proved to be adequate. Histories are unreliable guides for deciding whether or not an individual may be carrying the icterogenic agent in his blood. Later, it was found that the agent is heat resistant and is not inactivated by exposure to a temperature of 56° C. for one-half hour.

As the vaccine contained viable (attenuated) virus, the suspicion that the outbreak of jaundice following vaccination was yellow fever arose at once. Only those who had to deal with the situations can appreciate the alarm, fears, and stress which this suspicion aroused among civilian and military health officers in the Mississippi Valley in the spring of 1942. The dread of epidemic yellow fever, recalling the disaster of 1878, was oppressive. Reassurance was available, during one stage of uncertainty, from the studies made earlier by members of the staff of the International Health Division of the Rockefeller Foundation. They had shown that, although active yellow fever virus appeared for a short time in the blood of men and animals vaccinated with the 17D strain, it could not be spread by *A. aegypti* mosquitoes fed upon such subjects.<sup>19</sup>

As may be readily appreciated, the outbreak of postvaccinal hepatitis in the Army in 1942 not only affected military operations but also involved in-

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<sup>19</sup> Smithburn, K. C.: Immunology. In *Yellow Fever*. (George K. Strode, editor.) 1st edition. New York: McGraw-Hill Book Co., Inc., 1951.



numerable relationships of the highest importance within the Army and the Government. It was of major concern to relations with health officers of the States and with military and civilian officials overseas.<sup>20</sup>

### Quarantine

Quarantine against yellow fever and other diseases was a field of major concern to the Preventive Medicine Service. Colonel Knies<sup>21</sup> has reported at length on the problems, regulations and administration, and the complexities of the national and international relations involved when worldwide military operations come into contact with the civilian commerce, politics, and health protection policies of foreign countries. One section of the chapter deals with yellow fever quarantine. It is so complete that little needs to be added here.

The main differences with respect to yellow fever quarantine were between the requirements of the Government of India, with its associated agencies, such as the British Inter-Departmental Committee on Yellow Fever Control,<sup>22</sup> and the requirements which the United States regarded as scientifically justified and reasonable. Colonel Knies covers these differences in detail. Suffice it to note here that until 1944 the Indian Government required for entry from or through an endemic area of yellow fever (1) vaccination 16 days previously, and (2) revaccination at the end of 2 years. The opinion of the Preventive Medicine Service based upon reports and advice from Dr. Sawyer (p. 359) was that immunization could be considered to be established 10 days after vaccination and lasted for 4 years or longer. Convinced on both points, The Surgeon General desired to remove this hindrance to troop movements toward India and resisted a foreign regulation that would have required revaccination of the military forces in 1943 and thereafter.

There were prolonged negotiations over these differences of policy. From 1941 to 1943, the negotiations were conducted through the Department of State, without results and with great loss of time. Later, arrangements were made for direct communication and personal conferences in this country and abroad. In the midst of the difficulties, in 1943, a high official of the General Staff said to this author that he thought that "after all the matter was a technical dispute between doctors, and had better be settled directly." This appreciation of the fact that troop movements, cargo shipments, and travel of many persons might depend upon data and statements emanating from humble scientific laboratories was most welcome, though belated. This point of view facilitated the development of the foreign quarantine program as a whole. It led directly to favorable adjustments with India through the visit of General Simmons to

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<sup>20</sup> See footnote 16, p. 367.

<sup>21</sup> See footnote 9, p. 364.

<sup>22</sup> See footnote 8, p. 362.

New Delhi in 1943,<sup>23</sup> and with Great Britain and Egypt through the visits of this author to London in 1943<sup>24</sup> and to Cairo in 1944.<sup>25</sup>

The opinion of the Preventive Medicine Service with respect to immunization against yellow fever has been amply supported by the results of further investigations of the International Health Division of the Rockefeller Foundation, which was the scientific guide throughout the controversy. Summarizing the present knowledge on the subject, K. C. Smithburn<sup>26</sup> has stated that protective antibodies occur in the blood of human beings 10 days after vaccination against yellow fever, that the protective antibodies induced by the virus-vaccine usually persist for at least 6 years, and that it seems not unlikely that the immunity is as enduring (possibly lifelong) as that evoked by an attack of yellow fever.

## SUMMARY

In this chapter, an attempt has been made to summarize modern knowledge of yellow fever and to show its relation to the yellow fever control program of the Army. In doing so, the chapter has been prepared, in part, as a supplement to the basis chapters on immunization and foreign quarantine by Long and Knies, respectively. In supplementing those chapters, additional material has been added to the accounts of both the general and specific aspects of the preventive program and the events of its operation. The opinion is ventured that all the main elements of the program were necessary and that the program was carried out effectively and beneficially, even at the cost of the outbreak of postvaccinal hepatitis in 1942. No doubt the operation prevented some occurrence and spread of yellow fever and diminished risks to health. Whether it prevented the introduction of yellow fever into India and the Far East is a claim that no one can make with assurance. No one really knows the nature of the barrier that keeps yellow fever out of those regions. Therefore, it behooves officials of preventive medicine and quarantine to be reserved and curious before this mystery, trusting that it may conceal some principle yet to be discovered which when known will immensely strengthen protection against disease.

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<sup>23</sup> Brig. Gen. James S. Simmons visited New Delhi and conferred with representatives of the Indian Government as well as with military authorities, during August and September 1943. There were numerous communications from General Simmons to The Surgeon General, U.S. Army, for the Preventive Medicine Service, dealing with policies and regulations for vaccination against yellow fever. Of these, two of the most general and important were radiograms CM-IN-16119, 22 Sept. 1943, and CM-IN-16172, 22 Sept. 1943.

<sup>24</sup> Reports, Col. S. Bayne-Jones, MC, to The Surgeon General, U.S. Army, dated 28 Dec. 1943 and 7 Feb. 1944, subject: Yellow Fever Quarantine Regulations.

<sup>25</sup> Memorandum, Brig. Gen. S. Bayne-Jones, Deputy Chief, Preventive Medicine Division, for The Surgeon General (Through Chief, Preventive Medicine Service), 24 Apr. 1944, subject: Modification on Egyptian Government's Regulations on Yellow Fever Vaccination.

<sup>26</sup> See footnote 19, p. 368.

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